Kinetics and mechanisms of the formation and reactions of alkyl nitrites

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KINETICS AND MECHANISMS OF THE FORMATION AND REACTIONS OF ALKYL NITRITES.

BY

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A thesis submitted for the degree of Doctor of Philosophy in the University of Durham.

To my Parents

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Memorandum.

The work described in this thesis was carried out in the University of Durham between October 1978 and June 1981 and has not been submitted for any other degree. It is the original work of the author except where acknowledged by reference.

ABSTRACT.

The work in this thesis is concerned with the kinetics and mechanisms of reactions involving O-nitrosation.

The introductory chapter provides a brief survey of the literature concerning nitrosation at nitrogen, oxygen and sulphur.

The first experimental chapter deals with the kinetics of O-nitrosation in aqueous acidic solution leading to the formation of alkyl nitrites. Equilibrium constants for the formation of the alkyl nitrites were measured together with rate constants for the forward and reverse reactions. Rate and equilibrium constants were also determined for some carbohydrates.

The involvement of alkyl nitrites as possible nitrosating agents in aqueous alcoholic solutions containing acids and sodium nitrite was also investigated. The results obtained demonstrated that these nitrosation reactions occur via nitrous acid and the alkyl nitrites are almost totally ineffective as nitrosating agents. The effect of other additives (which could, in theory, form O-nitroso or S-nitroso species) on the nitrosation of amines was also investigated.

In order to draw a comparison between O- and S-nitrosation the formation of a thionitrite in dilute aqueous acid was investigated.

Alkyl nitrites have also been used in the past as nitrosating agents in non-aqueous solvents. In this thesis the kinetics of nitrosation reactions effected by an alkyl nitrite in alcohol solvent were also investigated.

CONTENTS.

CHAPTER ONE

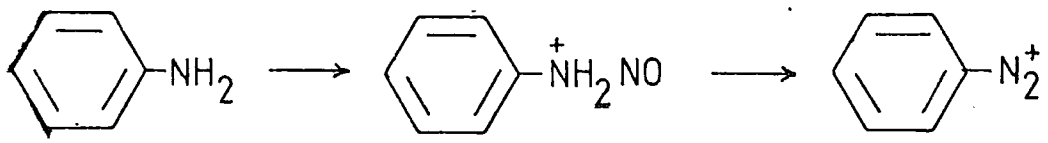
INTRODUCTION

1.1. Diazotisation and N-nitrosation.

1.1.1. Introduction.

Aromatic diazo compounds were discovered by Griess[1] in 1858 when he isolated the diazotised form of picramic acid as the product of a reaction in which he aimed to replace the amino group of the picramic acid by an hydroxyl group. At about the same time, but working independently of Griess, Mene[2] also discovered the reaction forming diazoaminobenzene from aniline and nitrous fumes. Griess' method of forming diazo compounds was soon replaced by simpler methods such as that of Martius[3] which used sodium nitrite as the source of the nitrosating agent. The historical development of diazotisation reactions has been recorded in several reviews.[4,5,6]

Bamberger[7] proposed that diazotisation proceeded via the formation of a primary N-nitrosamine (Scheme 1); this suggestion was later shown to be correct. Kalatzis and Ridd demonstrated that the diazotisation of aniline and the N-nitrosation of N-methylaniline had similar rate expressions.[8]



Scheme 1

It is now known that molecular nitrous acid exists in a series of equilibria with several inorganic nitrosating agents. It is thought that molecular nitrous acid is not sufficiently reactive to react with amines. The other possible nitrosating agents in increasing order of reactivity are given below:

$$N_2O_3 < NOHal < H_2NO_2^+ < NO^+$$

In perchloric or sulphuric acid only the nitrosyl ion, nitrous

acidium ion or nitrous anhydride could be active as nitrosating agents but in the presence of halide ions the formation of the nitrosyl halides becomes very important.

1.1.2. Diazotisation and nitrosation in the absence of halide ions.

The kinetics of diazotisation were first investigated by Hantsch and Schumann[9] who showed that the reaction was overall of the second order. Since there were only two reactants they assumed that the reaction was first order with respect to each reactant and that the reaction proceeded via the protonated form of the amine in spite of having no real evidence that this was the case.

Taylor[10] studied the deamination of methylamine and other reactions involving N-nitrosation and observed third order kinetics (second order with respect to nitrous acid). He suggested that the third order rate expression could be associated with a reaction proceeding via rate determining N-nitrosation. Schmid also confirmed the third order form of the rate expression (equation 1).[11]

$$\text{rate} = k[HNO_2]^2[\text{amine}] \qquad 1$$

Hammett, in 1940, proposed that the third order reaction was due to reaction between the free amine and nitrous anhydride (Scheme 2).[12] This mechanism was later confirmed by Hughes and Ridd[13].

$$2HNO_2 \underset{\text{fast}}{\rightleftharpoons} N_2O_3 + H_2O$$

$$ArNH_2 + N_2O_3 \xrightarrow{\text{slow}} ArNH_2NO^+ + NO_2^-$$

$$ArNH_2NO^+ \xrightarrow{\text{fast}} ArN_2^+$$

Scheme 2.

The intermediate primary N-nitrosamine has been detected spectroscopically at low temperatures (-70°C)[14].

The second and third order rate expressions proposed by the two groups of workers is explained by considering that each group were working at different acidities. Hantsch and Schumann worked with solutions of 0.002M perchloric acid at which acidity the concentration of unprotonated aniline would be sufficiently high to react with nitrous anhydride before any significant amount of the nitrous anhydride could be hydrolysed so that the rate determining stage of the reaction would be shifted from the reaction of the free amine with nitrous anhydride to the self-dehydration of molecular nitrous acid. In this case the rate expression would then be given by equation 2.

$$\text{rate} = k[HNO_2]^2 \qquad 2$$

Hantsch and Schumann were unable to distinguish between a reaction of second order in nitrous acid and one of first order with respect to each reactant.

In more recent work, Bunton, Llwellyn and Stedman have studied the rate of 18-oxygen exchange in solutions of low acidity and high nitrite concentration[15]. They found the reaction to be second order with respect to the nitrous acid and in good agreement with the rates of diazotisation according to equation 2.

The rate coefficient for the reaction between nitrous acid and the free aniline has been estimated to be ca. 10^7 l mol^{-1} s^{-1},[16] which is somewhat lower than the value expected for a reaction subject to diffusion control (ca. 9×10^9 l $mol^{-1}s^{-1}$ at 25 °C). Nitrous anhydride is

only weakly electrophilic and does not appear to react with the deactivated amines such as p-nitroaniline[17]. Since nitrous anhydride does not react with the protonated form of amines the observed rate constants for nitrosation and diazotisation reactions involving nitrous anhydride would be expected to decrease with increasing acidity. This is found to be the case for increases in acidity up to about 0.5M perchloric acid after which further increases in acidity produceincreases in the observed rate constants, k_o. Indeed it is found that k_o is proportional to the hydrogen-ion concentration and a new, acid catalysed reaction is indicated.

The rate expression for the acid catalysed reaction was found to obey equation 3.

$$\text{rate} = k[\text{amine}][HNO_2]h_o \qquad 3.$$

Hughes et alia[18] proposed that the new acid catalysed mechanism of diazotisation involved rate determining reaction of the nitrous acidium ion, $H_2NO_2^+$, with the free amine as shown in Scheme 3.

$$HNO_2 + H^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} H_2NO_2^+$$

$$ArNH_2 + H_2NO_2^+ \xrightarrow{\text{slow}} ArNH_2NO^+ + H_2O$$

$$ArNH_2NO^+ \xrightarrow{\text{fast}} ArN_2^+ + H_2O$$

Scheme 3

Since proton transfers to oxygen are rapid processes, the inorganic pre-equilibrium cannot be made rate-determining,

unlike the nitrous anhydride reaction.

On making further increases in the acidity of the medium, the observed rate constant is found to be almost independent of the acidity since an increase in h_o decreases the concentration of the free amine. However, for the more basic amines such as aniline the catalysis by acid is rather more marked and this has been interpreted as a reaction involving rate-determining attack of the nitrous acidium ion upon the protonated amine[19,20].

At much higher acidities, the observed rate constant reaches a maximum at ca. 6M perchloric acid and then decreases rapidly as the acidity is increased. The rate expression (equation 4) was found to be consistent with a mechanism outlined in Scheme 4 in which the proton loss of the protonated nitrosamine to the solvent becomes rate determining[21].

$$\text{rate} = k[ArNH_3^+][NO^+]h_o^{-2} \qquad 4$$

$$ArNH_3^+ + NO^+ \underset{\text{fast}}{\rightleftharpoons} ArNH_2NO^+ + H^+$$

$$ArNH_2NO^+ \xrightarrow{\text{slow}} ArNHNO + H^+$$

$$ArNHNO \xrightarrow{\text{fast}} ArN_2^+ + OH^-$$

Scheme 4

1.1.3. Diazotisation and nitrosation in the presence of halide ions.

Schoutissen reported in 1936 that hydrochloricacid had a catalytic effect on the diazotisation of aniline[22]. Schmid studied the effect of added chloride[23] and bromide ions[24] on the same reaction and found it to be subject to halide ion catalysis according to the rate expression given in equation 5.

$$\text{rate} = k[\text{amine}][H^+][HNO_2][Hal^-] \qquad 5$$

The involvement of the nitrosyl halide in the reaction was proposed by Hammett[12]; he proposed the mechanism outlined in Scheme 5.

$$HNO_2 + H^+ + Hal^- \overset{\text{fast}}{\rightleftharpoons} NOHal + H_2O$$

$$NOHal + ArNH_2 \xrightarrow{\text{slow}} ArNH_2NO^+ + Hal^-$$

$$ArNH_2NO^+ \xrightarrow{\text{fast}} ArN_2^+ + H_2O$$

Scheme 5

Diazotisation and nitrosation by nitrosyl halides becomes the predominant mechanism at quite low halide ion concentrations. For example, the nitrosyl chloride mechanism is the main mechanism of the diazotisation of aniline in 0.1M hydrochloric acid[17]. As in the case of the nitrous anhydride mechanism, the first stage of the nitrosyl halide mechanism does not involve the amine and, in theory, could be made rate-determining; this has not been reached for diazotisation by nitrosyl chloride, but it has been possible

to adjust conditions so that the formation of nitrosyl bromide and nitrosyl iodide becomes rate determining[25]. Under such conditions, the rate determining stage is considered to be the attack of the halide ion on the nitrous acidium ion.

The equilibrium constants for the formation of nitrosyl chloride and nitrosyl bromide have been determined at several temperatures[26,27,28] and using these values, the true rate coefficients (equation 6) for the reaction between the free amine and the nitrosyl halide has been calculated by Schmid[27,28,29].

$$\text{rate} = k[\text{amine}][\text{NOHal}] \qquad 6$$

In recent years there has been much interest in the subject of encounter-controlled reactions and the subject is discussed in detail in a review by Ridd[30]. The values of k obtained by Schmid and co-workers were all in the region $1\text{-}3 \times 10^9$ l $mol^{-1}s^{-1}$ together with the calculated activation energies for the reaction indicated that the reaction could be subject to diffusion control. Thompson[31] has also measured the rate constants for the diazotisation of various anilines, by nitrosyl chloride and bromide using stopped-flow spectrophotometry and his results are in fairly good agreement with the values obtained by Schmid. Thompson and Williams[32] studied the variation of the true rate constants with the basicity of the amines and it was found that as the basicity of the amines increased the rate coefficient approached the diffusion controlled limit of ca. 7×10^9 l $mol^{-1}s^{-1}$ for aqueous solutions at 25°C. So for amines such as p-methylaniline and p-anisidine the

rate of reaction would appear to be close to the diffusion controlled limit.

In arguments based upon principles of the electro - negativity of the halogens, it would be expected that nitrosyl chloride would be more reactive than nitrosyl bromide which in turn would be more reactive than nitrosyl iodide. However the catalysis of nitrosation by halide ions increases in the sequence

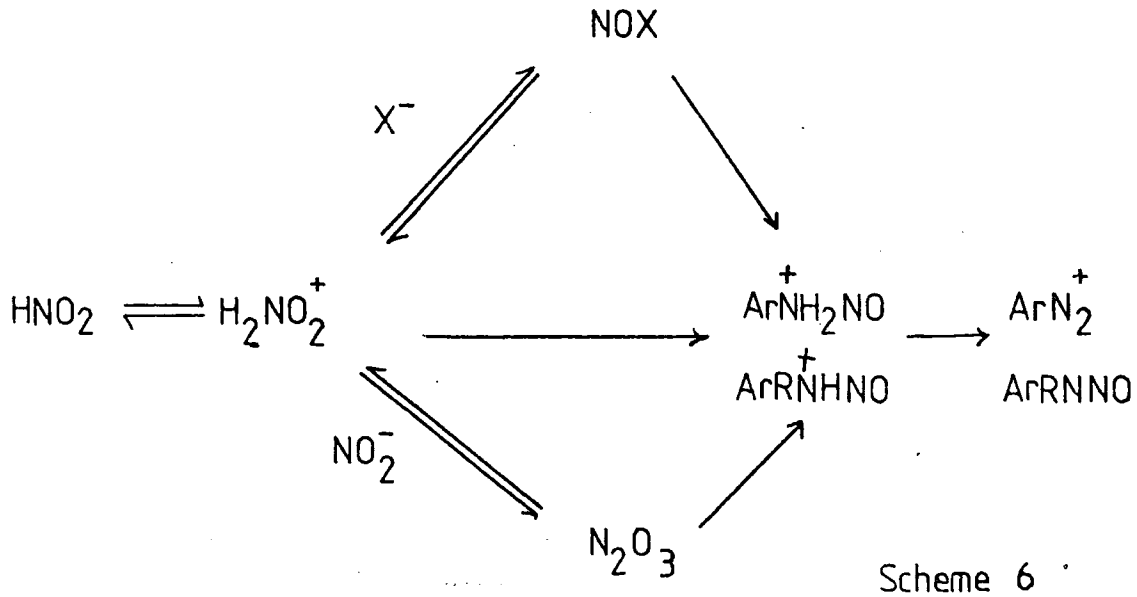
$$Cl^- < Br^- < I^-$$

The equilibrium constants for the formation of the nitrosyl halides from nitrous acid also follow the above sequence. This enables one to understand why the formation of nitrosyl chloride could not be made rate limiting; it would not be possible to adjust reaction conditions such that the concentration of nitrosyl chloride would be high enough to make the rate of reaction with the amine faster than the rate of formation of nitrosyl chloride.

More recently it has been recognised that N-nitrosation reactions may be catalysed by nucleophiles other than halide ions, in particular by sulphur nucleophiles such as thiocyanate ion[33,34,35] and thiourea[34,35].

1.1.4. Summary of diazotisation and N-nitrosation.

For diazotisation and N-nitrosation reactions at low acidities (i.e. less than 0.5M hydrogen ion concentration) the possible reaction mechanisms may be represented by Scheme 6 below:



Scheme 6

For secondary aromatic amines the reaction results in the formation of the corresponding N-nitrosamine; for primary aromatic amines the product of the reaction is the corresponding diazonium ion. The N-nitrosation of secondary aliphatic amines also follows the mechanisms outlined in Scheme 6[36,37].

In alcoholic solutions it appears that in the presence of chloride[38,39] or bromide ions[39] the diazotisation of anilines involves the nitrosyl halide and possibly the alkyl nitrite. Whether the alkyl nitrites act as direct nitrosating agents has not been established and it is one of the aims of the present work to solve this problem.

It appears that Scheme 6 would also apply to

nitrosation reactions other than diazotisation and N-nitrosation. For example, Stedman[40] has found that some of the reactions outlined in the scheme also apply to the reaction between nitrous acid and hydrazoic acid. Bunton, Dahn et alia have studied the nitrosation of ascorbic acid a reaction apparently involving O-nitrosation and again reactions appear to parallel those in Scheme 6.[41]

1.2. Denitrosation of N-nitrosamines.

1.2.1. Denitrosation and the Fischer-Hepp rearrangement.

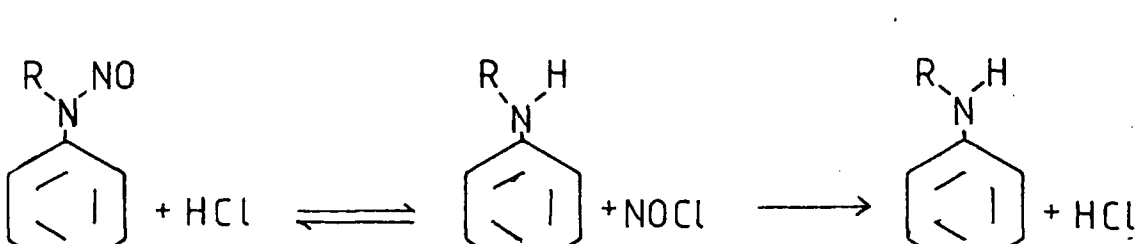
N-nitrosamines readily undergo denitrosation to yield the corresponding secondary amine in the presence of acid and a 'nitrite trap' such as sulphamic acid, azide ion, etc.. In some of the early work, MacMillan and Reade achieved the denitrosation of nitrosamines in hydrochloric acid in the presence of urea or thiourea[42]. Jones and Kenner successfully denitrosated nitrosamines by heating them with cuprous chloride and hydrochloric acid[43].

In the absence of nitrite traps, aromatic N-nitrosamines undergo the Fischer-Hepp rearrangement[44] to the corresponding para-C-nitrosamine concurrently with denitrosation, the proportion of each product being dependent upon the experimental conditions (for example the yield of the product of rearrangement could be maximised by the use of solutions of hydrogen chloride in ethanol[45]).

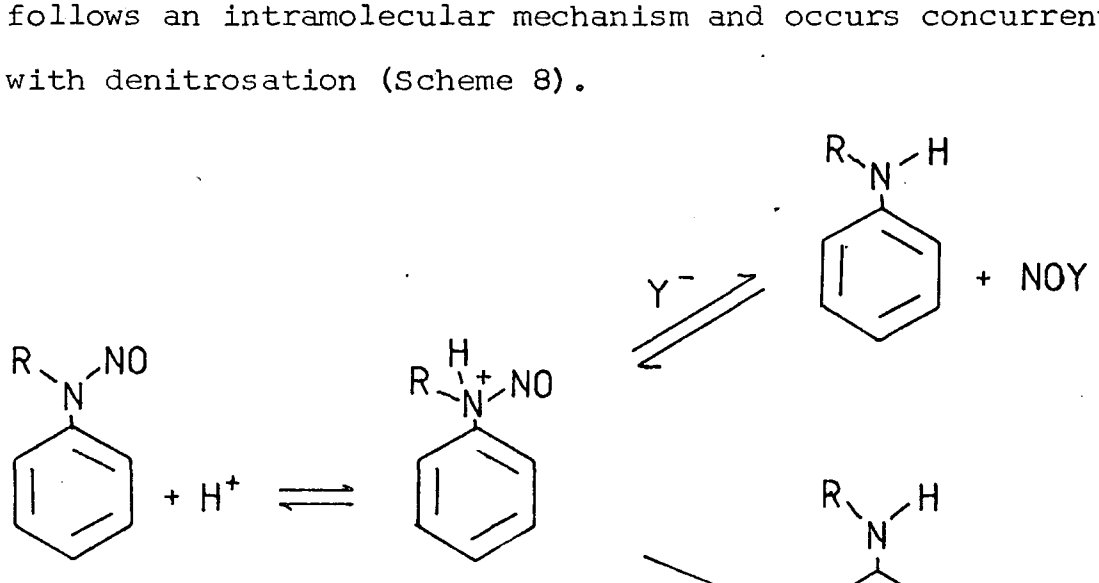
There has been much debate on the relationship between denitrosation and rearrangement of aromatic N-nitrosamines and whether the rearrangement occurred by an inter- or an intramolecular mechanism. In 1913, Houben[46] proposed that reaction occurred by an intermolecular rearrangement

involving the nitrosating agent produced by the denitrosation of the nitrosamine. This mechanism (Scheme 7) was accepted until recently.

Scheme 7



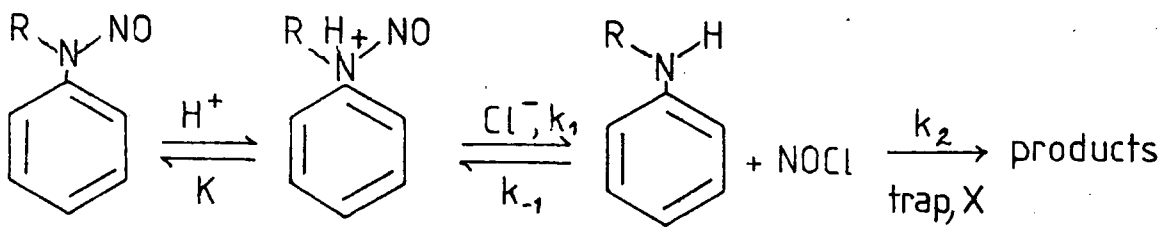
The intermolecular rearrangement was doubted largely because rearrangement still occurred even in the presence of a large excess of nitrite traps[47,48,49]. However it has now been established using kinetic methods[50] that the reaction follows an intramolecular mechanism and occurs concurrently with denitrosation (Scheme 8).



Scheme 8

1.1.2. The mechanism of denitrosation.

It is possible to study the denitrosation reaction of aromatic N-nitrosamines without complications due to the reversibility of the first step in Scheme 8 if reactions are carried out in the presence of an excess of a nitrite trap. Quantitative denitrosation may be obtained in the presence of an excess of nitrite trap and an efficient nucleophile. The reaction is acid catalysed and the mechanism for denitrosation was suggested to follow Scheme 9.



Scheme 9

The experimentally determined first order rate coefficient, k_o (defined by equation 7) may be expressed by equation 8 if a Hammett type dependence for the protonation of the nitrosamine is assumed and the principle of stationary states is applied to the nitrosyl halide concentration.

$$-\frac{d[ArRNNO]}{dt} = k_o[ArRNNO] \qquad 7$$

$$k_o = \frac{k_1 k_2 K h_o [Cl^-][X]}{k_{-1}[ArNHR]+k_2[X]} \qquad 8$$

In the presence of a large excess of trap X, then the inequality

$$k_2[X] >> k_{-1}[ArNHR]$$

applies and equation 8 reduces to equation 9.

$$k_o = k_1 K h_o [Cl^-] \qquad 9$$

Therefore in the presence of a large excess of trap, the denitrosation process may be studied without the complications of the reversibility of the denitrosation step. Equation 9 indicates that the denitrosation reaction should be subject to nucleophile and acid catalysis. Catalysis by chloride ion and acid was demonstrated for the denitrosation of N-methyl N-nitrosoaniline in aqueous hydrochloric acid by Biggs and Williams[51]; they found that k_o was proportional to the product $(k_o[Cl^-])$ up to 5M hydrochloric acid. Solvent isotope studies supported a mechanism involving fast protonation of the nitrosamine followed by rate determining nucleophilic attack upon the nitroso-nitrogen. By working in aqueous sulphuric acid and adding various nucleophiles Biggs and Williams also demonstrated that plots of k_o against the concentration of nucleophile were linear and hence obtained values of the product k_1K for chloride, bromide, thiocyanate and iodide ions. Plots of $(\log k_1K)$ against Swain and Scott's 'n' values[52] were linear and demonstrated that the denitrosation of N-nitrosamines was highly dependent upon the reactivity of the nucleophile. In aqueous solutions the order of reactivity is

$$I^- \gtrsim SCN^- > Br^- > Cl^- > H_2O$$

The order of efficiency of various nitrite traps towards the nitrous acidium ion or nitrosyl chloride has been demonstrated by Williams[49] for the denitrosation of N-methyl N-nitrosoaniline (NMNA):

$$HN_3 = \text{hydrazine} > NH_2SO_3H > NH_2OH > \text{urea}$$

Biggs and Williams have investigated the denitrosation of NMNA in the presence of limiting concentrations of various traps and varying the acidity[53]. The results demonstrated that at acid concentrations below 5.5M hydrochloric acid k_o was linear with respect to h_o but at higher acidities the linear relationship broke down either due to extensive protonation of the trap (for the less reactive traps) or to the extensive protonation of the nitrosamine.

For the denitrosation of N-alkyl N-nitrosamines in the presence of halide ions the effect of varying the nature of the alkyl group has been investigated[54]. The rate of denitrosation was found to increase in the sequence

$$Me < {}^{t}Bu \simeq {}^{n}Pr < Et \ll {}^{i}Pr$$

N-t-butyl N-nitrosoaniline appeared to show anomalously low reactivity; this was thought to be due to steric factors. The sequence may be due to the differing basicities of the nitrosamine and or the operation of steric factors.

In the case of ring substitution at the 3 and 4 positions the nitrosamines show a small range of reactivity which has been interpreted as the combination of two opposing effects - the effect of ring substitution on the nitroso-nitrogen and on the basicity of the nitrosamine. In aqueous sulphuric acid in the absence of halide ions the

sequence of reaction rates for 4-substitution are:

$$Cl < H < CH_3 < OCH_3$$

This suggests that the nitrosamine is attacked by a positively charged species, now accepted to be H_3O^+.

In the presence of halide ions the sequence of reaction rates is exactly reversed, indicating that the nitrosamine is subject to nucleophilic attack.

For the denitrosation of diphenylamine at high azide concentrations it was found that the first order rate constant became independent of the bromide ion concentration (at high bromide ion concentrations) and a change in the solvent isotope effect was observed[55]. The results suggested that at low bromide ion concentrations the rate determining stage is the nucleophilic attack on the protonated nitrosamine but at high bromide ion concentrations the rate determining stage shifts to the initial protonation of the nitrosamine. It has been found that anilines catalysed the denitrosation of N-nitrosodiphenylamine due to the formation of a π-type complex between the protonated nitrosamine and the protonated aniline.

Challis and Osborne have studied the reactions of N-nitrosodiphenylamine with various traps in order to distinguish between direct and indirect transnitrosation[56]. For reaction with the various traps such as urea, azide ion, hydrazine, hydroxylamine or sulphamic acid it was regarded that nitrosyl carriers (NOY) were important. However with N-methylaniline in place of a trap, there

was no nucleophilic catalysis, suggesting direct transnitrosation and they postulated a mechanism involving a tetrahedral intermediate. These reactions between N-nitrosodiphenylamine and N-methylaniline would, however, have been complicated by the reversibility of the N-methylaniline nitrosation. Thompson[57] has overcome this problem by studying the diazotisation of aniline using N-nitrosodiphenylamine. In this case, the primary nitrosamine intermediate would undergo a fast irreversible reaction to produce the diazonium ion. In the presence of high trap concentrations distinction between direct and indirect transnitrosation reactions could be made by kinetic methods. It was found that direct nitrosation of aniline and its derivatives occurred but with the two primary aliphatic amines studied (n-butylamine and cyclohexylamine) direct nitrosation did not take place.

1.2.3. Denitrosation of N-nitrosoamides and related species.

N-alkyl N-nitrosamines follow a denitrosation mechanism involving fast initial proton transfer followed by rate determining N-N bond fission except at high nucleophile concentrations in which case the initial protonation becomes rate determining. N-nitrosoamides, however, undergo denitrosation in which the initial protonation is slow, irrespective of the concentration of the nucleophile[58,59,60].

Challis and co-workers have studied the acid catalysed denitrosation and deamination of N-n-butyl N-nitrosoacetamide[58] and N-nitroso 2-pyrrolidone[59] and

found that the reaction was independent of the concentration of nucleophile. From their results they concluded that the reaction involved the slow initial protonation of the nitrosoamide as the rate determining step.

in a study of the denitrosation of N-ethyl N-nitrosourethane, Thompson demonstrated the independence of the observed rate constant on the concentrations of azide ion, chloride ion, bromide ion and N-ethylurethane[57]. In the absence of added trap or nucleophile the denitrosation was rapid and the yield of nitrous acid was only about 70% of the maximum theoretical yield. The reaction of N-ethyl N-nitrosourethane resembled the denitrosation of certain nitrosoamides which undergo concurrent deamination[58,59].

Williams has studied the kinetics of the denitrosation of N-methyl N-nitrosotoluene p-sulphonamide (MNTS) in aqueous acidic solutions[60]. It was found that MNTS, contrary to the denitrosation of N-ethyl N-nitrosourethane, underwent quantitative denitrosation, the reaction was first order with respect to the MNTS and acid concentrations but was independent of the concentrations of traps, N-methyl toluene p-sulphonamide and nucleophile. The reaction appeared to parallel the reactions of N-nitrosoamides and contrasts with observations on the denitrosation of N-nitrosamines. These observations appear to be the result of the effect of the strong electron-withdrawing effect of the SO_2 group

It appears that for N-nitrosocompounds with substituents such as -SOOR, -$CONH_2$, -COR, -COOR, the slow

initial protonation of the N-nitroso compound is a consequence of the weak basicity of these compounds.

1.2.4. denitrosation involving sulphur nucleophiles.

there is presently much interest in denitrosation reactions involving sulphur nucleophiles. S-nitrosation is involved in such reactions and the subject is reviewed later in this chapter (section 1.4.).

1.2.5. denitrosation in non-aqueous solvents.

DENITROSATION IN ETHANOL.

Johal and Williams[61] have investigated the denitrosation of two N-nitrosamines (N-methyl N-nitrosoaniline and N-nitrosodiphenylamine) and one N-nitrosoamide (MNTS) in ethanolic hydrogen chloride. For the nitrosamines it was found that the reactions were reversible in the absence of nitrite traps and the position of the equilibrium was dependent upon the hydrogen chloride concentration. Rate constants were obtained for the forward reaction in the presence of an excess of nitrite trap (ascorbic acid) and the rate law given in equation 10 was established.

$$\text{rate}' = k[\text{nitrosamine}][HCl] \qquad 10$$

In the absence of ascorbic acid, N-nitrosodiphenylamine underwent the Fischer-Hepp rearrangement; the rate constant for rearrangement was much less than that for denitrosation at the same acidity.

The denitrosation of the N-nitrosamide was found to be irreversible even in the absence of a nitrite trap.

The denitrosation of all three compounds was not catalysed by bromide or thiocyanate ion, and the solvent isotope effects were consistent with a mechanism in which proton tranfer to the nitrosamine was rate determining.

In aqueous ethanol, the rate of denitrosation of N-methyl N-nitrosoaniline was found to decrease as the proportion of water in the solvent was increased and nucleophilic catalysis was seen to come into operation. It was found that reactions in less than 95% ethanol showed the same behaviour as in aqueous solution. Dix[62] found that in 98% ethanol reactions showed intermediate behaviour, i.e. catalysis by some nucleophiles (chloride and bromide ion) but not by others (thiocyanate ion) was observed.

DENITROSATION IN OTHER SOLVENTS.

Dix[62] has also studied the denitrosation of N-methyl N-nitrosoaniline in other solvents, namely DMSO, DMSO/water, acetic acid and acetic acid/water mixtures.

In DMSO reactions were found to be similar to those in aqueous solution although DMSO appeared to behave as a better solvent and produced significant enhancements in the rate of reaction.

In glacial acetic acid rates of denitrosation were too high to be measured by conventional techniques. However, in aqueous acetic acid the results indicated that the solvent was a good one for the denitrosation reaction, but thiourea was found to show an anomalously low catalysis.

1.2.6. N-nitrosamines and carcinogenisis.

In recent years the potency of N-nitrosamines as carcinogens has become apparent[63]. The toxicity of N-nitrosamines was recognised as a result of industrial accidents involving dimethylnitrosamine[64] (which was used as a solvent) and N-methyl N-nitrosourethane[65]. Later it was shown that N-nitrosamines formed by the reaction of sodium nitrite and secondary amines present in fishmeal were responsible for the development of tumours in animals which had been fed on the nitrite-preserved meal[66].

It has been found that the organs affected by the nitrosamine depends upon the structure of the nitrosamine and also upon the species of animal involved (see for example the review by Ember[67]). The carcinogenic activity of nitrosamines appears to depend upon the ability of the nitrosamine to behave as a methylating agent although their mode of action is not known in detail.

N-nitrosamines occur in small amounts in the environment. Secondary amines capable of being nitrosated are widespread in foodstuffs, pesticides and pharmaceuticals and when ingested together with a source of nitrite (such as nitrite in preserved meat or in water) in the stomach there is the possibility of the formation of N-nitrosamines.

It is important to study the chemistry of N-nitrosamines as carcinogens and the possibility of man's exposure to them. In particular it is important to investigate the conditions under which nitrosamine formation is favoured and to determine the conditions

which could inhibit their formation.

1,3. O-nitrosation and the chemistry of alkyl nitrites.

1.3.1. Introduction.

Alkyl nitrites are readily generated and also readily hydrolysed[68], but until recently few mechanistic studies had been made on reactions involving O-nitrosation. Alkyl nitrites are usually prepared by the reaction between nitrous acid and the corresponding alcohol[69] (equation 1).

$$ROH + HNO_2 \rightleftharpoons RONO + H_2O \qquad 1$$

They are rather unstable but when dry may be stored in a refrigerator for a matter of weeks.

Alkyl nitrites have been widely used as nitrosating agents in syntheses[70], One of the earlier references to their use being the diazotisation of anilines using amyl nitrite by Knoevenagel[71]. They have proved to be of greatest use in reactions where the use of nitrous acid has been unsuitable.

Reactions in which alkyl nitrites undergo thermal and photochemical decomposition by homolytic fission have been studied in detail but their heterolytic reactions have so far received little attention.

1.3.2. The acid and base catalysed hydrolysis of alkyl nitrites.

Alkyl nitrites undergo rapid hydrolysis via acid or base catalysed reactions. Fischer correctly pointed out that the acid catalysed hydrolysis of ethyl nitrite was too

rapid to be studied using any of the kinetic methods available at the time[72]; the base catalysed reaction was known to be a little slower.

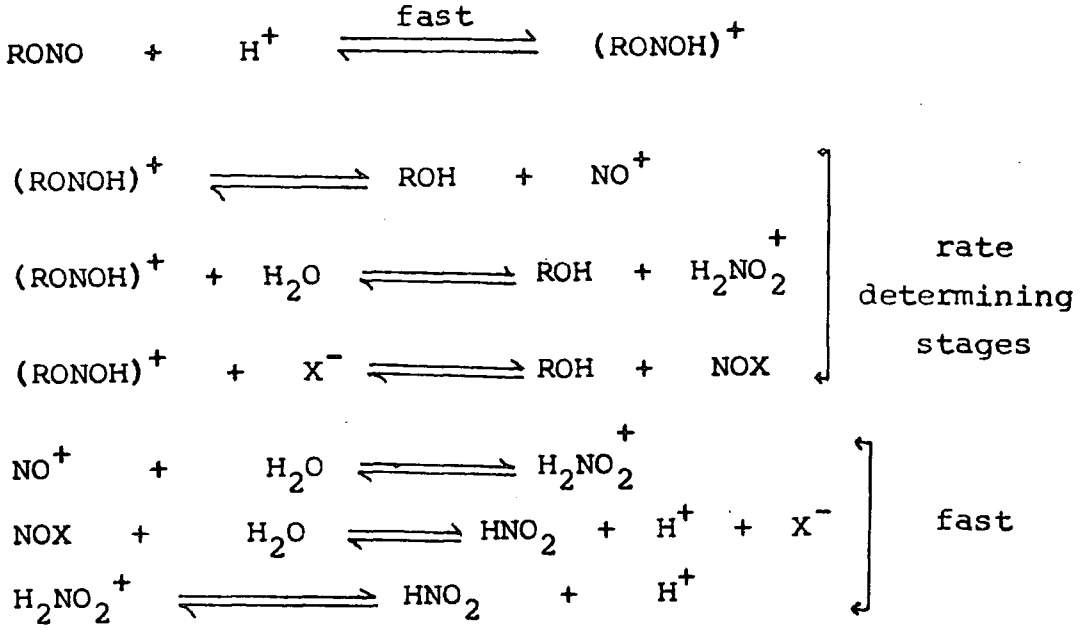
Allen[73] has made a kinetic study of the acid and base catalysed hydrolysis of some alkyl nitrites in dioxane-water solvent at 0°C. In dilute perchloric acid (0.001 to 0.007M) the rate expression for the hydrolysis of n-propyl nitrite was established (equation 11).

$$-\frac{d[nPrONO]}{dt} = k[H^+][nPrONO] \qquad 12$$

The hydrolysis was also found to be subject to catalysis by chloride and bromide ions. The acid catalysed hydrolysis of t-butyl nitrite and diphenylmethyl nitrite was also studied. t-Butyl nitrite was found to hydrolyse about 2-3 times faster than n-propyl nitrite; the results for diphenylmethyl nitrite gave rather inaccurate rate constants due to difficulty in obtaining a sufficiently pure sample of the ester.

Allen also carried out ^{18}O-exchange experiments for the hydrolysis of t-butyl nitrite and experiments using an optically active alkyl nitrite ((-)-1-methylheptyl nitrite) in order to demonstrate that the acid catalysed hydrolysis proceeded exclusively by nitrosyl-oxygen fission.

In order to account for the experimental observations Allen proposed the following mechanism (Scheme 10).



Scheme 10

The acid catalysed hydrolysis of alkyl nitrites is much fasterthan for the corresponding carboxylic acid esters. This may be accounted for by the relative positions of the initial protonation equilibria since the rate determining stages have rate constants that are proportional to the concentration of the protonated ester.

The alkaline hydrolysis of n-propyl nitrite and t-butyl nitrite in aqueous dioxane at 25-55^{o}C were also studied by Allen. For a given temperature and reaction conditions n-propyl nitrite hydrolysed some fifty times as rapidly as t-butyl nitrite. From experiments on the hydrolysis of optically active alcohols, Allen concluded that the alkaline hydrolysis of alkyl nitrites proceeded by nitrosyl-oxygen fission and involved nucleophilic attack of the hydroxyl ion on the nitrogen atom of the ester.

Oae et alia have compared the alkaline hydrolysis of

nitrites and carboxylic esters[74]. They noted the following differences between the two reactions:

1 alkaline hydrolysis was much faster for the carboxylic ester.

2 acid catalysed hydrolysis was much faster for the alkyl nitrite.

3 for the alkaline hydrolysis of n-hexyl nitrite no oxygen exchange took place[75]

4 polar substituent effects on the leaving group in carboxylic esters were larger than those in alkyl nitrites.

5 entropies of activation for alkaline hydrolysis of alkyl nitrites were greater than for the carboxylic esters.

6 steric factors for the reaction in alkaline conditions were lower for the alkyl nitrites.

These differences were rationalised by consideration of the centres of attack - the nitrogen of the alkyl nitrite would be more electronegative than the carbon of the carboxylic esters and the nitrogen posesses a lone pair which the carbon atom does not have.

Kobayashi[76] has reported that oxygen exchange does occur for both the acid and alkaline hydrolysis of i-amyl nitrite with ^{18}Oxygen labelled water; he explained this on the basis of the addition-elimination mechanism of ester hydrolysis proposed by Bender[77]. Kobayashi's results however, conflict with results of oxygen exchange experiments of other groups of researchers.

1.3.3. Nitrosation of alcohols by nitrosyl halides.

The nitrosation of alcohols by nitrosyl chloride in non-aqueous solvents has been the subject of recent studies by two groups of workers. The reactions are rapid and require the use of stopped-flow spectrophotometry to enable kinetic studies to be made.

Dalcq and Bruylants[78] made a study of the equilibrium between alcohols, nitrosyl chloride and alkyl nitrites (equation 12) in glacial acetic acid. They determined the equilibrium constants for various alcohols, rate constants

$$ROH + NOCl \underset{}{\overset{K}{\rightleftharpoons}} RONO \qquad 12$$

for the forward and reverse reactions and studied the effect of substituents on the equilibrium. They reported that electron donating substituents shifted the equilibrium to the right by enhancing the basicity of the alcohol and stabilising the alkyl nitrite. They also concluded that steric effects on the equilibrium were rather weak and explained this by considering the relatively small size of the nitrosyl group.

In a recent study, Napoleone and Schelly[79] have made thermodynamic and kinetic studies of the reaction of nitrosyl chloride with n-butanol in carbon tetrachloride-acetic acid mixtures. Equilibrium measurements were made using conventional spectrophotometric methods and kinetic studies were made using solvent-jump stopped-flow spectrophotometry. Equilibrium constants determined via rate constants were found to agree with those determined by the other method.

In their study of the diazotisation of anilines, Woppmann and Sofer[39] have made kinetic studies of the reaction in methanol solvent and estimated the equilibrium constants for the methanol, nitrosyl bromide(or nitrosyl chloride), methyl nitrite equilibria at $0^{o}C$.

1.3.4. Base catalysed reactions of alkyl nitrites with amines.

The reaction of some alkyl nitrites with amines in basic media has been the subject of some mechanistic studies.

Oae et alia[80] studied the aminolysis of phenethyl nitrite in aqueous alkaline dioxane. Reactions were shown to be overall of the second order (with the exception of the reaction with trimethylamine which showed autocatalysis by the trimethylammonium ion) and no general base catalysis was observed. Rates of reaction were found to increase in the sequence

$$NH_3 < CH_3NH_2 < (CH_3)_2NH < (CH_3)_3N$$

Plots of log k against $pK_{BH}+$ for the reaction were scattered; Oae rationalised this by considering that the substitution of a hydrogen atom by a methyl group would produce a marked increase in the nucleophilicity. Plots of log k against the vertical ionisation potential were, however, linear.

Oae compared his findings with the aminolysis of phenethyl acetate and concluded that the reaction of phenethyl nitrite would proceed by way of a concerted mechanism rather than an addition-elimination reaction.

Challis and Shuker have reported that in basic media β-substituted alkyl nitrites behaved as efficient nitrosating agents towards the nitrosation of amines[81]. They found that simple alkyl nitrites appeared to be quite ineffective as nitrosating agents in alkaline conditions; this was demonstrated by reactions of gaseous nitrosyl chloride, nitrous anhydride or dinitrogen tetroxide with piperidine in the absence and presence of simple alcohols such as methanol, ethanol, t-butanol. It was reported that the addition of these alcohols reduced the yield of product by approximately 90% by forming the corresponding alkyl nitrite. Polyhydric alcohols were shown to have a different effect; initially the concentration of product was lowered but then slowly increased with time to give a quantitative yield. Similar effects were reported for nitrosation reactions in the presence of trifluoroethanol, β-fluoroethanol, $(HOCH_2CH_2)_3N$, glucose and mannose.

1.3.5. Acid catalysed reactions involving alkyl nitrites

Schmid, Woppmann and co-workers have made studies on the acid catalysed diazotisation of aniline in methanol. In these reactions it is possible that methyl nitrite could be involved.

For diazotisation in methanolic hydrogen chloride Schmid and Muhr[38] established the rate equation and deduced that the rate determining step was the reaction of the free aniline with nitrosyl chloride. Later, Woppmann and Sofer[39] studied the diazotisation in methanolic

hydrogen chloride and hydrogen bromide and established the equilibrium constants for the equilibrium between the nitrosyl halides and methanol. Woppmann[82] has also studied the diazotisation of aniline derivatives in methanolic hydrogen halides.

In all these studies the behaviour of the methyl nitrite has not been clearly established. The nitrite could behave as a direct nitrosating agent or could act indirectly via the formation of the nitrosyl halide or nitrous acid (in aqueous solutions). One of the aims of the present work is to establish the mode of behaviour of alkyl nitrites as nitrosating agents.

Schmid and Riedl developed an indirect method for the determination of the equilibrium constants for the formation of alkyl nitrites in aqueous solution[83]. The method was based upon the nitrosation of phenols in aqueous alcoholic solutions. They noticed that small additions of simple alcohols produced marked reductions in the rate of nitrosation of phenol. Equilibrium constants for the formation of the alkyl nitrites and rate constants for the O-nitrosation of the alcohols were deduced and shown to decrease in the sequence

$$MeOH > iPrOH > tBuOH$$

This was rationalised on the basis of increasing steric hinderance.

Kricsfalussy et alia have published a series of papers on the kinetics of reactions of the butyl nitrites with aliphatic amides in solvents of various dielectric

constants[84,85,86]. The rate equation was shown to be first order with respect to the amide and the alkyl nitrite. It was found that n-butyl nitrite showed a different type of SN_2 reaction to the other butyl nitrites (this was indicated by n-butyl nitrite having a p^*(Taft) value of the opposite sign to the other nitrites). Rate constants were also shown to be dependent on the nature of the solvent but no simple correlation was established.

Shenton and Johnson[87] have made a study of the N-nitrosation of sulphanilamide with cyclohexyl nitrite. At low acidity reactions were found to be of second order with respect to the nitrite concentration and independent of the amide concentration whereas at higher acidity a first order dependence on the amide concentration and a second order dependence on the nitrite was observed. The results of kinetic studies indicated that the nitrosation of sulphanilamide by cyclohexyl nitrite involved the initial hydrolysis of the nitrite followed by the nitrosation of the amide by an inorganic nitrosating agent.

In the present work it is aimed to study the formation of alkyl nitrites in aqueous acidic solutions in the presence and absence of halide ions by direct methods. It is also necessary to establish beyond reasonable doubt whether alkyl nitrites can behave as direct nitrosating agents or whether their behaviour as nitrosating agents is dependent upon their first undergoing hydrolysis (or attack by nucleophiles) to yield an inorganic nitrosating agent.

The existence of O-nitroso species in the nitrosation

of other compounds containing an hydroxyl group and the effect of such compounds on N-nitrosation reactions are to be investigated.

1.4. Reactions involving S-nitrosation.

1.4.1. Introduction.

Thiols react readily with nitrous acid or other nitrosating agents to yield the corresponding thionitrite, RSNO, in a reaction analogous to the formation of alkyl nitrites from alcohols[88]. Thionitrites tend to be unstable[89] but a few stable thionitrites are known, in particular triphenyl thionitrite[90] and S-nitroso N-acetyl (D,L)penicillamine[91]. Thionitrites generally posess a characteristic red colouration[88,92] although both the stable thionitrites mentioned earlier are dark green. Thionitrites undergo both thermal and photochemical decomposition to yield the corresponding disulphide (equation 13).

$$2\ RSNO \longrightarrow RSSR + 2\ NO \qquad 13$$

The possible involvement of S-nitrosation in both N-nitrosation and denitrosation reactions was mentioned earlier. The importance of S-nitrosation is now reviewed in greater depth.

1.4.2. Nitrosation reactions involving sulphur nucleophiles

The catalysis of N-nitrosation reactions by thiocyanate ion[33,34,35] and thiourea[34,35] has been established. The catalytic activity of such species is due to the formation of nitrosyl thiocyanate and the S-nitroso adduct with

thiourea. The activity of thiocyanate ion has been found to be somewhere between that of bromide ion and iodide ion, while for thiourea the activity was almost as great as iodide ion.

Stedman et alia[93] have studied the kinetics of the nitrosation of thiourea and have determined the equilibrium constant for the reaction to be ca. 5000 l^2mol^{-2} at 25°C and have determined the rate constant for the S-nitrosation step.

The equilibrium constant for the formation of nitrosyl thiocyanate has also been determined by Stedman and Whincup[94] to be 32 l^2mol^{-2} at 20°C. These values are indeed much larger than the values for nitrosyl chloride[27] and nitrosyl bromide[28] ($1.1x10^{-3}$ and $5,1x10^{-2}$ l^2 mol^{-2} at 25°C respectively).

Meyer and Williams[35] have shown that the catalytic efficiency of thiourea towards the N-nitrosation of morpholine and the diazotisation of aniline is largely due to the magnitude of the equilibrium constant for the formation of the nitrosyl-thiourea adduct rather than the efficiency of the cation as a nitrosating agent towards the amines. It was also pointed out that other sulphur compounds may show a similar catalytic activity although they found that cysteine showed no such behaviour and S-methyl cysteine only showed a weak ability to catalyse the diazotisation of aniline.

Stedman et alia have also investigated the reaction of nitrous acid with cysteine and some alkyl thioureas[95].

In these cases S-nitrosations were also rapid and reported to be encounter controlled processes; the nitrosation of cysteine was found to be quantitative.

The possibility now arises that thiols having very large equilibrium constants for their nitrosation but which show no catalytic activity towards N-nitrosation could behave as nitrite traps and thus inhibit nitrosamine formation. Indeed this subject is currently of great interest to the food industry since thiol species such as cysteine have been used as food additives and could possibly be added safely to foodstuffs in the aim of preventing N-nitrosamine formation.

Dennis,McWeeny and co-workers have made studies on the transnitrosation reaction between S-nitrosocysteine and secondary amines[96,97]. They showed that the reaction did take place but in acidic conditions the rate of reaction was much lower than nitrosation with nitrous acid.

A small section of the present work seeks to determine whether thiols could inhibit N-nitrosation reactions and to study the kinetics of nitrosation of a thiol.

1.4.3. S-nitrosation and the denitrosation of N-nitrosamines

There is much interest in denitrosation reactions involving sulphur nucleophiles. Stedman et alia observed yellow colourations of solutions of nitrous acid and thiourea[93]. Earlier, Werner observed that more concentrated solutions produced red colourations[98]. Williams has reported that the same yellow colouration was seen in reactions

between thiourea and N-methyl N-nitrosoaniline and he proposed the formation of an unstable adduct between the nitrosyl cation and thiourea as an intermediate in the reaction[99]. In a preliminary report, the reactivity of thiourea towards NMNA was stated to be somewhere between that of bromide ion and iodide ion[100]. Williams reported that thiourea reacted with NMNA to yield N-methylaniline and the S-nitrosothiourea cation[99]. It was also demonstrated that the S-nitroso species was also able to react as a direct nitrosating agent since the addition of N-methyl aniline reduced the rate of reaction; this also indicates the reversibility of the formation of the S-nitroso species from the nitrosamine and the thiourea.

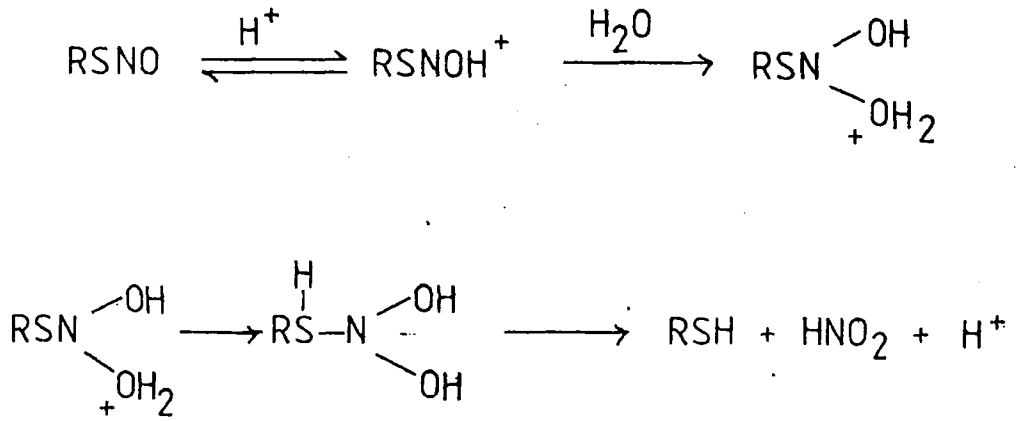
In more recent work, Hallett and Williams[101] have demonstrated the catalysis of denitrosation of NMNA by some alkylthioureas and in these cases S-nitrosation was believed to occur. All the thioureas were shown to have similar reactivities towards the protonated nitrosamine. In the same study cysteine was found to have a reactivity about the same as chloride ion; glutathione also had about the same reactivity. However for the S-methyl derivatives such as S-methyl cysteine and methionine the reactivity was increased to approximately the same reactivity as bromide ion.

1.4.4. The denitrosation of thionitrites.

Ooi[102] has made a study of the denitrosation of two thionitrites (N-acetyl S-nitrosocysteine and N-acetyl S-nitroso (D,L) penicillamine) in aqueous solution.

Reactions were sensitive to light and atmospheric oxygen. The effect of irradiation and the addition of various compounds was investigated.

The decomposition of S-nitrosocysteine was found to be faster in high and low pH rather than in neutral conditions; reactions in basic conditions were more rapid than in acidic media. Denitrosation was also subject to nucleophilic catalysis. The following mechanism (Scheme 11) was proposed in which nucleophilic attack on the nitrogen was rate determining for the reaction in acidic conditions.



Scheme 11

In basic media, the nucleophilic attack on the thionitrite was also suggested as being rate determining. Similar mechanisms were suggested for the denitrosation of N-acetyl S-nitroso (D,L) penicillamine.

CHAPTER TWO

KINETICS OF NITROSATION OF ALCOHOLS AND SUGARS.

2.1. Introduction.

Upon mixing aqueous solutions of sodium nitrite and an alcohol in dilute acid the equilibrium between nitrous acid and the alkyl nitrite is rapidly established (equation 2.1). Indeed the reactions occur too rapidly to be followed by conventional kinetic methods; however, kinetic measurements are accessible by employing the technique of stopped-flow spectrophotometry. The technique is described in the experimental details at the end of this chapter (section 2.5).

$$ROH + HNO_2 \overset{K}{\rightleftharpoons} RONO + H_2O \qquad 2.1$$

Since alkyl nitrites are frequently used as synthetic reagents in aqueous conditions, it would be of interest to investigate the mechanism of the formation of alkyl nitrites and to determine the rate constants for the forward and reverse processes by direct methods.

In the present study it was decided to examine the acid and halide ion catalysed reactions of methanol and then to extend the study to other alcohols and compounds containing the hydroxyl functional group - to carbohydrates for example.

Two recent studies have been made on the formation of alkyl nitrites under non-aqueous conditions.

Dalcq and Bruylants[78] studied the reaction of ten alcohols with nitrosyl chloride at 20°C in glacial acetic acid. The reactions were found to be rapid but could be followed by using the stopped-flow technique. From their kinetic measurements the following rate law was established:

$$\text{rate} = k_2[\text{ROH}][\text{NOCl}] + k_3[\text{ROH}]^2[\text{NOCl}] - k_{-2}[\text{RONO}][\text{HCl}] - k_{-3}[\text{RONO}][\text{HCl}][\text{ROH}]$$

With the exception of methanol, it was found that this rate law could be simplified to

$$\text{rate} = k_2[\text{ROH}][\text{NOCl}] - k_{-2}[\text{RONO}][\text{HCl}]$$

Rate constants were determined for the reaction; the derived equilibrium constants were shown to be rather insensitive to steric effects but were affected more by electronic effects and hyperconjugation. The lack of sensitivity towards steric effects was interpreted on the basis of enhanced solvation of the sterically hindered alcohols. Rate constants were larger for alcohols containing electron-donating substituents; this was accounted for as the increased nucleophilicity of the alcohols. Dalcq and Bruylants suggested that hyperconjugation effects would stabilise the alkyl nitrites by producing greater charge delocalisation in the O-nitroso group.

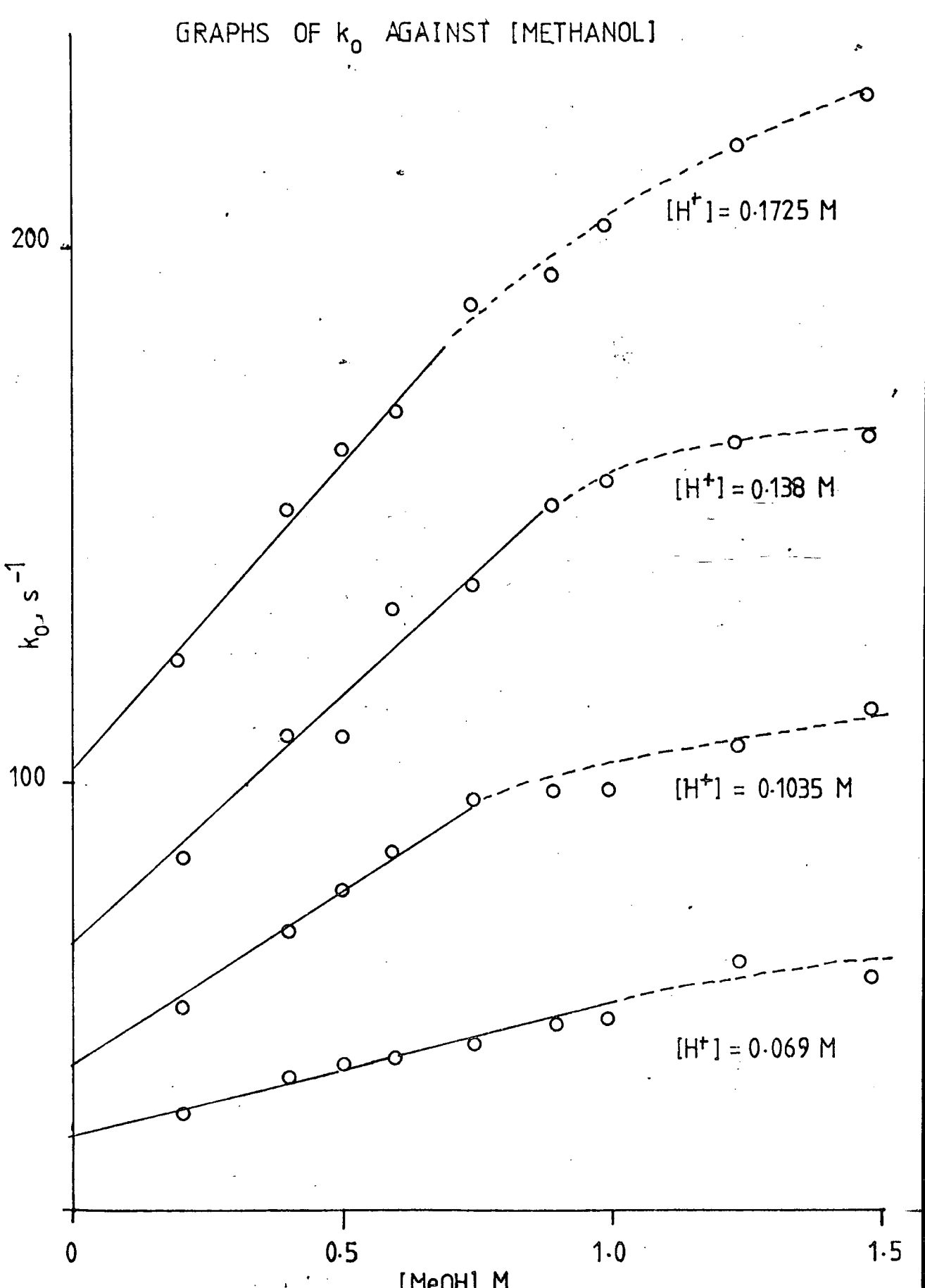
More recently, Napoleone and Schelly[79] have studied the reaction between nitrosyl chloride and n-butanol in pure carbon tetrachloride and in acetic acid-carbon tetrachloride solvent mixtures by use of a modified stopped-flow technique (solvent-jump). For the equilibrium

$$\text{NOCl} + \text{nBuOH} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{nBuONO} + \text{HCl}$$

the rate constants for the forward and reverse processes were determined and the equilibrium constants were found from the ratio of k_1 to k_{-1}. Equilibrium constants were found to be in good agreement with the values determined

FIGURE 1.

GRAPHS OF k_0 AGAINST [METHANOL]



by optical measurements. Series of experiments were carried out at two temperatures and the activation energies for both processes together with standard thermodynamic quantities were calculated.

2.2. The acid catalysed nitrosation of alcohols.

2.2.1. The nitrosation of methanol.

In this study, preliminary experiments indicated that the equilibrium constant for the formation of methyl nitrite was significantly larger then for the nitrite esters of the other simple alcohols. The near ultraviolet spectrum of methyl nitrite showed more marked differences to that of nitrous acid than the other simple alkyl nitrites[103]. The combination of these two factors led to the conclusion that the nitrosation of methanol would be the easiest reaction to study.

Working with experimental conditions such that the methanol was present in large excess over the nitrous acid kinetic measurements (made by following the change in absorbance at 386nm on a Canterbury stopped-flow spectrophotometer at a temperature of 0^{o} or $25^{o}C$) showed good first order behaviour, the first order rate constant, k_o, being defined by equation 2.2. Since the changes in

$$-\frac{d[HNO_2]}{dt} = k_o\left([HNO_2] - [HNO_2]_{eq}\right) \qquad 2.2$$

absorbance were rather small and the reactions very rapid, kinetic runs were repeated five times and the mean rate coefficient taken as k_o. The dependence of k_o on the methanol concentration was studied at various sulphuric acid concentrations. In all kinetic runs the nitrite

concentration was 0.04M. The results for the variation of k_o with changing methanol concentration are presented in tables 2.1. to 2.4 in section 2.6 of this chapter (most tables of experimental results are collected in this section). The results are also shown graphically in figure 1.

The graphs of k_o against the methanol concentration showed two significant features. Firstly that plots of k_o against the methanol concentration were linear provided the methanol concentration did not exceed approximately 0.6M; at concentrations abovethis the rate constants were lower than expected. This could well be attributed to the solvent effect caused by the considerable methanol concentration. Secondly, the graphs had positive intercepts, indicating the reversible nature of the reaction being studied. The slopes and intercepts of the linear portions of the graphs are quoted in the table below. The results also indicate that the reaction is subject to acid catalysis. Indeed, plots of k_o against the hydrogen ion concentration (i.e. the hydrogen ion concentration remaining after making allowance for the removal of hydrogen ions by the formation of nitrous acid, assuming full protonation of the nitrite ion) were linear and through the origin. The acid catalysis

Graphs of k_o against [methanol].

$[H^+]$ x10^2,M.	slope, l $mol^{-1}s^{-1}$ k_2	intercept, s^{-1} k_{-1}
6.9	26.4 ± 4.2	33.6 ± 1.9
10.35	73.1 ± 0.7	43.7 ± 0.3
13.80	90.2 ± 7.2	70.2 ± 4.4
17.25	120 ± 6	101 ± 3.

of the formation of methyl nitrite in aqueous perchloric acid at 25°C has also been demonstrated (table 2.5). Plots of k_o against the hydrogen ion concentration for the perchloric acid and the sulphuric acid (table 2.6) catalysed reactions were shown to have the same slopes (within the limits of experimental error) and zero intercepts.

At methanol concentrations below ca. 0.6M k_o may be expressed by equation 2.3 where k_2 is the second order rate coefficient for the forward reaction (given in rate

$$k_o = k_2[MeOH] + k_{-1} \qquad 2.3$$

expression 2.4) and k_{-1} is the first order rate coefficient for the reverse reaction (rate expression 2.5).

$$\text{forward rate} = k_2[MeOH][HNO_2] \qquad 2.4$$

$$\text{reverse rate} = k_{-1}[MeONO] \qquad 2.5$$

It is clear, therefore, that the values of k_2 and k_{-1} may be obtained from the slope and intercept respectively of the graphs of k_o against the methanol concentration. Since graphs of k_o against the hydrogen ion concentration were linear, catalysis by hydrogen ions of both the forward and reverse reactions is indicated and so k_o may be expressed by equation 2.6 where k_3 is the third order rate constant for the forward reaction and k_{-2} is the second order rate

$$k_o = k_3[MeOH][H^+] + k_{-2}[H^+] \qquad 2.6$$

constant for the reverse reaction so that the rate expressions for the forward and reverse reactions are:

$$\text{forward rate} = k_3[MeOH][H^+][HNO_2]$$

$$\text{reverse rate} = k_{-2}[MeONO][H^+]$$

Thus the values of k_3 and k_{-2} may be determined via the

graphs of k_o against the methanol concentration. The mean values obtained at 25°C were:

$$k_3 = 700 \pm 100 \text{ l}^2\text{mol}^{-2}\text{s}^{-1}$$

$$k_{-2} = 576 \pm 57 \text{ l mol}^{-1}\text{s}^{-1}$$

Values of k_3 and k_{-2} determined at each acidity are given in the table below. The ratio of the rate constants $k_3 : k_{-2}$ gives the equilibrium constant, K, for the equilibrium:

$$HNO_2 + MeOH \underset{}{\overset{K}{\rightleftharpoons}} MeONO + H_2O$$

K is defined by equation 2.7 and it is also clear that K is also given by the ratio of the slope to the intercept of the graph of k_o against the methanol concentration. Thus, K was determined at four acidities and the values are given below:

$$K = \frac{[MeONO]}{[MeOH][HNO_2]} = \frac{k_3}{k_{-2}} \qquad 2.7$$

$[H^+]_{xs}$ M	k_3 $\text{l}^2\text{mol}^{-2}\text{s}^{-1}$	k_{-2} $\text{l mol}^{-1}\text{s}^{-1}$	K l mol^{-1}
0.069	382 ± 60	487 ± 28	0.78 ± 0.17
0.104	706 ± 8	422 ± 3	1.67 ± 0.03
0.138	653 ± 52	508 ± 32	1.28 ± 0.17
0.172	695 ± 35	733 ± 18	1.19 ± 0.09

As stated previously, experimental conditions were such that the methanol was present in great excess over the nitrous acid and plots of $\ln(A_t - A_\infty)$ against time were strictly linear, indicating good first order behaviour with respect to nitrous acid. However, experiments intended to demonstrate the independence of k_o on the total nitrite concentration

revealed that k_o showed a small decrease upon increasing the nitrite concentration (after making allowance for the reduction in k_o produced by the decrease in the hydrogen ion concentration as a result of increasing the concentration of added nitrite ion). The results are shown in table 2.7 in which k_o is the experimentally observed rate constant and k_1 is the rate coefficient in which allowance has been made for the change in acidity. The small decrease in the rate constant k_1 may be due to a minor contribution to the rate by a process involving a second order dependence upon the nitrite concentration (i.e. nitrosation of methanol by nitrous anhydride). It must also be pointed out that in these reactions the methanol concentration was rather high.

The nitrosation of methanol in aqueous perchloric acid has also been studied at 0^oC. The data for the dependence of k_o on the methanol concentration are presented in table 2.8 and the data for the variation of k_o with the hydrogen ion concentration are given in table 2.9. The data were treated in the same way as for the reaction at 25^oC, that is, the values of k_3 and k_{-2} were determined via the slope and intercept respectively of a plot of k_o against the methanol concentration. The rate constants k_3 and k_{-2} were found to have values of $67.3 \pm 0.8\ l^2 mol^{-2} s^{-1}$ and $34.5 \pm 5.7\ l\ mol^{-1} s^{-1}$ respectively. Thus at a temperature of 0^oC the equilibrium constant for the formation of methyl nitrite, K, was found to have a value of $1.95 \pm 0.32\ l\ mol^{-1}$.

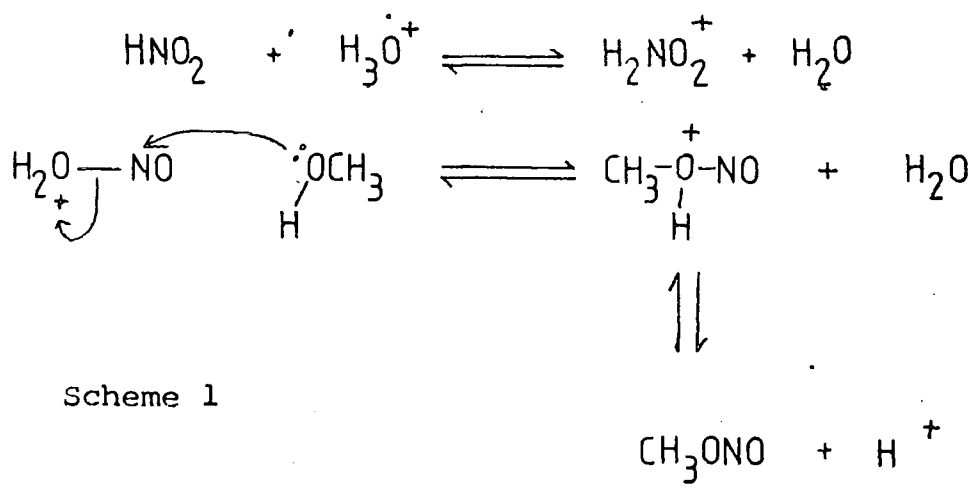
For the formation of methyl nitrite the confirmed rate law (equation 2.4) is consistent with a reaction

mechanism in which the rate determining stage is the attack of the nitrosating agent (which, in theory, could be either the nitrous acidium ion or the nitrosonium ion) upon the methanol. For the experimental conditions used in the present reactions the nitrosating agent would most probably be the nitrous acidium ion.

Bayliss and Watts have studied the nitrous acid system by spectroscopic methods[104,105,106]. In aqueous sulphuric and perchloric acids they found that the concentration of the species NO^+ only became significant at ca. 50% acid (by weight). Below this, there was no evidence for the presence of the nitrosonium ion. At above 70% acid the ultra violet spectrum was essentially that of NO^+.

It appears, therefore, that at the very low acid concentrations used in the present study the only important constituents of the solution would be molecular nitrous acid and a smaller amount of the nitrous acidium ion.

Therefore, the most likely mechanism for the reaction is outlined in Scheme 1 below:



Scheme 1

In 1958, Allen[73] made a study of the hydrolysis of alkyl nitrites. He prepared an optically active alkyl nitrite and demonstrated that it was hydrolysed with complete retention of configuration in aqueous acidified dioxan, implying that bond fission was taking place at the nitrosyl-oxygen bond. Moreover, he demonstrated that the formation of (+)-1-methyl heptyl nitrite from nitrous acid and (+)-octan-2-ol in aqueous solution occurred without racemisation thus demonstrating that the formation of alkyl nitrites involved O-nitrosation. Further experiments on the hydrolysis of t-butyl nitrite in ^{18}O-enriched water demonstrated that there was no enhancement in the ^{18}O content of the t-butanol and so established that the reaction again was one of nitrosyl-oxygen bond fission.

The rate coefficients k_3 determined in the present study for the nitrosation of methanol include the equilibrium constant, K, for the protonation of the nitrous acid and are therefore not true rate constants. However, from the values of k_3 determined at 0^oC and 25^oC it is possible to estimate the activation energy for the formation of methyl nitrite in water using the Arrhenius relationship between a rate constant, k, and the absolute temperature, T (equation 2.8).

$$\ln k = \ln A - \frac{E_a}{RT} \qquad 2.8$$

From a plot of ($\ln k_3$) against T^{-1} the activation energy was estimated as 62 kJ mol^{-1}. Although this estimate was made on the basis of two sets of data and can only be regarded as an approximate value, it is of interest to determine the activation energy for the nitrosation of

methanol and to discuss its magnitude in comparison to other nitrosation reactions.

Many acid catalysed nitrosation reactions (in particular the N-nitrosation of certain substituted anilines) are thought to be subject to diffusion control[30,32], the evidence for such control is largely based upon the independence of the values of the rate constants (equivalent to k_3) upon the nature of the substrate. Reactions suggested to be subject to diffusion control have characteristically low energies of activation. The activation energy determined for the formation of methyl nitrite includes ΔH° for the protonation of the nitrous acid. For the reaction between two neutralspecies the activation energy is typically 14 kJ mol^{-1} for a diffusion controlled process. For the reaction between one positively charged and one neutral species as is the case for the formation of methyl nitrite the activation energy would be a little different; for example, Stedman found the activation energy for the nitrosation of thiourea by the nitrous acidium ion, a process regarded as being diffusion controlled, to be 64.7 kJ mol^{-1} (reference 95). Therefore on this basis it appears that the nitrosation could be subject to diffusion control. However this conclusion is not supported by the rate constants. The values of the rate constants equivalent to k_3 for encounter controlled nitrosations of various substrates at $0^{\circ}C$ have been found to average at ca. 640 $l^2mol^{-2}s^{-1}$ (a few are listed in the table overleaf). This is almost ten times greater than the value of k_3 for the

Rate constants for nitrosation by the nitrous acidium ion[30].

substrate	T°C	k, $l^2 mol^{-2} s^{-1}$
o-chloroaniline	0	175
p-nitroaniline	0	161
O-methylhydroxylamine	0	184
O,N-dimethylhydroxylamine	0	225
2-methylindole	3	484
1,2-dimethylindole	3	530
2-phenylindole	3	650
thiourea	25(0)	6960(637)

nitrosation of methanol at 0°C. Therefore, one would conclude from arguments based upon the magnitudes of the rate constants k_3 that although the nitrosation of methanol does have a large rate constant, it does not appear to fall into the class of diffusion controlled reactions.

It would also have been of interest to determine the rate constant for the attack of water upon the protonated methyl nitrite. However, the value of this rate constant is inaccessible since the pK_a of methyl nitrite in water is not known.

2.3 O-nitrosation of other alcohols and carbohydrates.

In this section of the project the nature of the R group in compounds of formula ROH was varied and the resulting effect upon the kinetics was observed. Nine compounds were studied- ethanol, n-propanol, i-propanol, t-butanol, ethanediol, glycerol, mannitol, sucrose and glucose. In several cases, notably the carbohydrates, reactions were rather rapid for the stopped-flow technique but since absorbance changes at the available wavelengths were rather small ratesof reaction could not be reduced by the reduction of the concentrations of the reactants. The wavelengths selected for each alcohol are shown in the experimental section. All reactions were carried out under first order conditions using a large excess of the alcohol.

2.3.1. The nitrosation of ethanol.

For the nitrosation of ethanol rate and equilibrium measurements were made at $0^{o}C$ and $25^{o}C$.

Working at $25^{o}C$, the dependence of k_o upon the ethanol concentration was studied in aqueous sulphuric acid; the results are presented in table 2.10. A graph of k_o against the ethanol concentration was linear with a positive intercept (the slope and intercept are quoted in the table). The acid catalysis of the nitrosation of ethanol was also demonstrated (table 2.11) and the graph of k_o against the hydrogen ion concentration was linear with zero intercept.

Analysing the results in the same way as for the nitrosation of methanol, the ratio of the slope to the

intercept of the plot of k_o against the ethanol concentration gave a value of 0.58 ± 0.09 l mol^{-1} for the equilibrium constant for the formation of ethyl nitrite at 25°C. From the graph of k_o against the ethanol concentration the rate constants k_3 and k_{-2} were determined to be 173 ± 23 $l^2 mol^{-2} s^{-1}$ and 298 ± 9 l $mol^{-1} s^{-1}$ respectively. The equilibrium constant for the formation of ethyl nitrite at 25°C is somewhat smaller than that for the formation of methyl nitrite. It appears that the nitrosation of ethanol follows the same reaction mechanism as for the nitrosation of methanol since both reactions follow the same rate law.

The nitrosation of ethanol at 0°C was studied using solutions in aqueous perchloric acid. Data for the dependence of the first order rate coefficient, k_o upon the ethanol concentration are reported in table 2.12. Plotting k_o against the ethanol concentration gave a good straight line with a positive intercept (fig. 2); the slope and intercept of the line were calculated and from the ratio of the slope to the intercept the equilibrium constant for the formation of ethyl nitrite at 0°C was calculated to be 0.81 ± 0.10 l mol^{-1}. The rate constants k_3 and k_{-2} were determined from the slope and intercept, respectively, and their values estimated to be

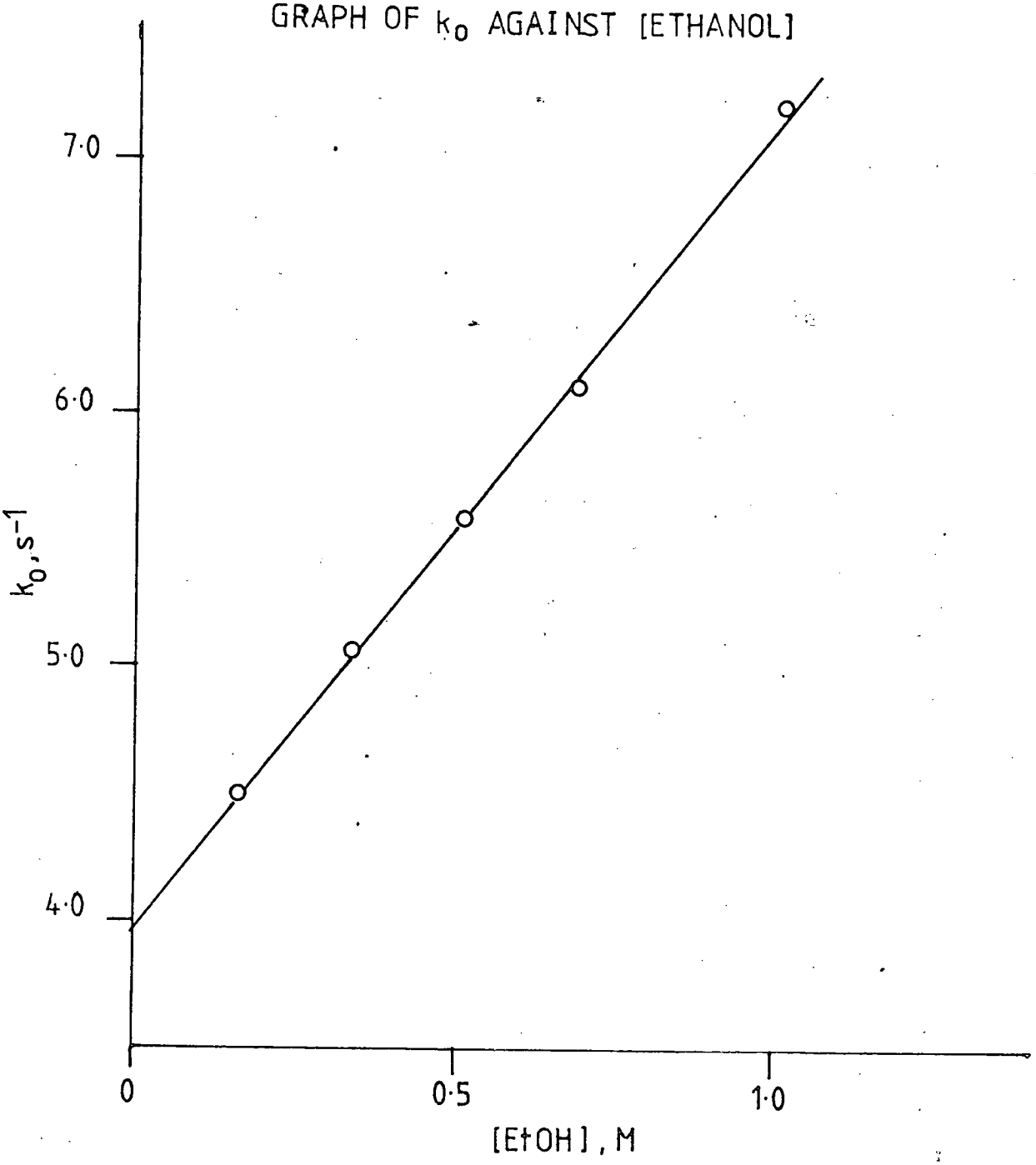
$$k_3 = 37.7 \pm 0.3 \ l^2 mol^{-2} s^{-1}$$

$$k_{-2} = 46.9 \pm 0.2 \ l \ mol^{-1} s^{-1}$$

From the values of the rate constant k_3 determined at the two temperatures, the activation energy, E_a, for the reaction between the nitrosating agent (nitrous acidium ion)

FIGURE 2

GRAPH OF k_o AGAINST [ETHANOL]



and ethanol was estimated to be ca. 61 kJ mol^{-1}; this is in good agreement with the activation energy determined for the methanol reaction.

On considering the magnitude of the rate constant k_3 for the nitrosation of ethanol and comparing them with the corresponding values for reactions that are considered to be subject to diffusion control, it is apparent that the nitrosation of ethanol does not fall into the classification of a diffusion controlled reaction. The nitrosation of ethanol appears to be very similar to the methanol reaction, and this is to be expected.

2.3.2. The nitrosation of n-propanol.

The formation of n-propyl nitrite was studied in aqueous perchloric acid at $0^{o}C$. Only the dependence of k_o upon the n-propanol concentration was investigated; it was thought unnecessary to demonstrate the linear dependence of k_o upon the hydrogen ion concentration for all the alcohols studied and so the acid catalysis was only demonstrated for a selection of alcohols.

For the dependence of k_o upon the n-propanol concentration (table 2.13) a graph of k_o against [n-propanol] revealed a linear plot with a positive intercept. The equilibrium constant for the formation of n-propyl nitrite was calculated from the ratio of the slope to the intercept as 0.66 ± 0.04 l mol^{-1}. The rate constants k_3 and k_{-2} were determined and found to have the following values:

FIGURE 3 - DEPENDENCE OF k_0 ON [i-PROPANOL]

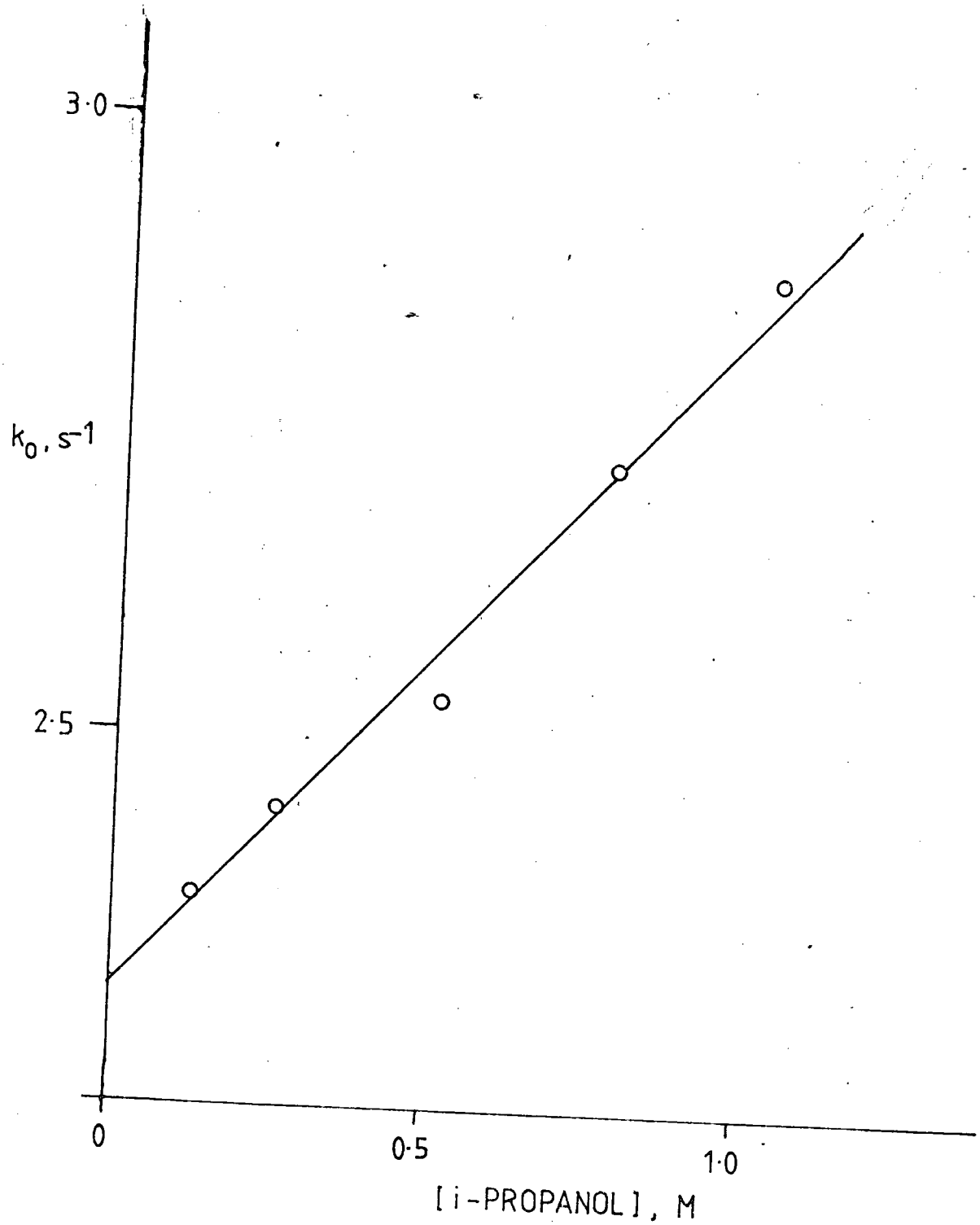
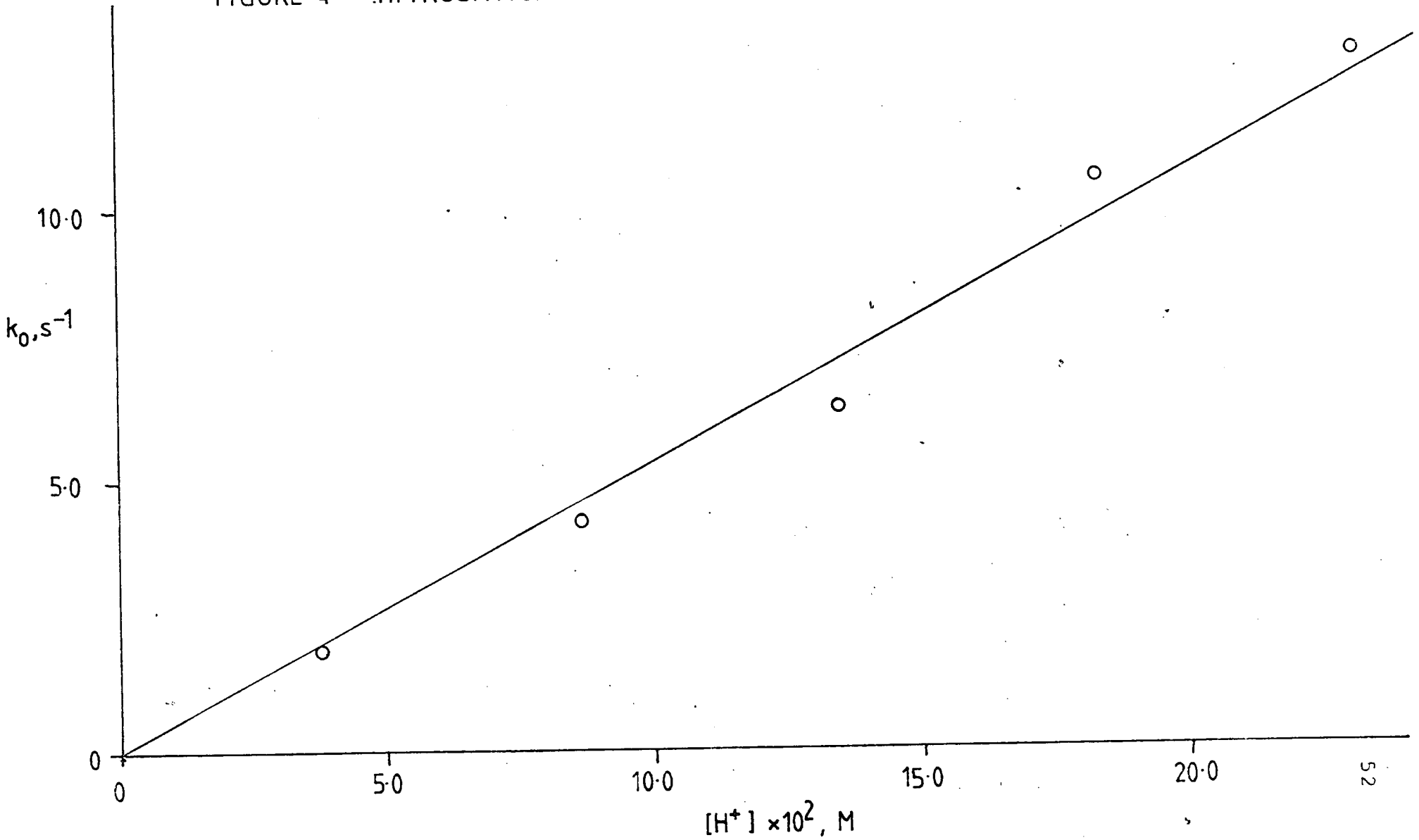


FIGURE 4 - NITROSATION OF i-PROPANOL, ACID CATALYSIS



$$k_3 = 29.3 \pm 1.1 \ l^2 mol^{-2} s^{-1}$$
$$k_{-2} = 44.1 \pm 1.0 \ l \ mol^{-1} s^{-1}$$

2.3.3 The nitrosation of i-propanol.

The nitrosation of i-propanol was studied at 0^oC in aqueous perchloric acid. The dependence of k_o on both the i-propanol and the hydrogen ion concentration were examined. The results for the variation of k_o with the i-propanol concentration are presented in table 2.14. A graph of k_o against the i-propanol concentration (fig. 3) showed a linear correlation; the graph had a large positive intercept and a rather small slope, indicating that the equilibrium constant for the formation of i-propyl nitrite was small. The equilibrium constant, given by the ratio of the slope to the intercept was found to be $0.22 \pm 0.02 \ l \ mol^{-1}$ at 0^oC. According to the expression for the rate constant k_o in terms of the rate constants for the forward and reverse reactions, the rate constants k_3 and k_{-2} were determined to be:

$$k_3 = 9.83 \pm 0.73 \ l^2 mol^{-2} s^{-1}$$
$$k_{-2} = 43.9 \pm 0.5 \ l \ mol^{-1} s^{-1}$$

The rate constant k_o was also shown to have a linear dependence upon the hydrogen ion concentration (fig. 4 and table 2.15).

2.3.4. The formation of t-butyl nitrite.

The nitrosation of t-butanol was investigated at 0^oC. It washoped to study the variation of k_o with the t-butanol concentration but it was appanent that the equilibrium

constant for the formation of t-butyl nitrite was too small to permit a significant change in the first order observed rate coefficient upon increasing the t-butanol concentration. In order to observe the reaction the concentration of t-butanol was required to be very high and the mean values of k_o obtained at two t-butanol concentrations were within the limits of experimental error of one another (table 2.16). Assuming that k_o may be expressed in terms of the rate constants for the forward and reverse processes:

$$k_o = k_2[tBuOH] + k_{-1}$$

and assuming $k_2[tBuOH] << k_{-1}$ the observed rate constant k_o gives an approximate value of k_{-1}. Thus, k_{-1} was ca. 5.7 s^{-1} and the second order rate constant for the reverse process, k_{-2}, was estimated to be 103 l $mol^{-1}s^{-1}$. Because the variation of k_o with the t-butanol concentration showed no trend it is only possible to state that the equilibrium constant for the formation of t-butyl nitrite in aqueous solution at 0°C is small compared to those of other alkyl nitrites (on the basis of the values of K for the other alkyl nitrites the value for t-butyl nitrite would be estimated to be less than 0.1 l mol^{-1}).

2.3.5. The nitrosation of ethanediol.

Rate constants for the nitrosation of ethanediol in aqueous sulphuric acid were determined at 25°C. The dependence of k_o on both the ethanediol and acid concentrations were studied. The data for the dependence of k_o on the ethanediol concentration at constant acidity are given in

table 2.17. A graph of k_o against the ethanediol concentration was linear with a positive intercept; the slope and intercept are quoted in the table. From the ratio of the slope to the intercept the equilibrium constant for the formation of the alkyl nitrite was calculated to be 1.38 ± 0.08 l mol^{-1} at 25°C. The rate constant k_3 for the nitrosation of ethanediol was calculated to be 460 ± 20 $l^2 mol^{-2} s^{-1}$ and the rate constant k_{-2} for the hydrolysis of the alkyl nitrite was determined as 332 ± 5 l $mol^{-1} 2^{-1}$.

The variation of k_o with the hydrogen ion concentration was studied at an ethanediol concentration of 0.269M. The results are presented in table 2.18. A plot of k_o against the hydrogen ion concentration was, as expected, found to be linear and through the origin.

2.3.6. Nitrosation of glycerol.

The nitrosation of glycerol was studied in aqueous sulphuric acid. The data for the variation of k_o with the glycerol concentration at 25°C and 0°C are presented in tables 2.19 and 2.20. Graphs of k_o against the glycerol concentration were linear; the slopes and intercepts are quoted in the tables.

Analysis of the results in the usual way provided the following values of the equilibrium constant for the formation of the alkyl nitrite

$$K = \begin{cases} 0.50 \pm 0.26 \text{ l mol}^{-1} \text{ @ } 0^\circ\text{C} \\ 0.84 \pm 0.08 \text{ l mol}^{-1} \text{ @ } 25^\circ\text{C} \end{cases}$$

The rate constants k_3 and k_{-2} were evaluated from the

slopes and intercepts of the graphs and their values are shown in the table below.

Rate constants for the nitrosation of glycerol.

$T^{o}C$	$k_3, l^2 mol^{-2} s^{-1}$	$k_{-2}, l\ mol^{-1} s^{-1}$
0	42.7 ± 3.2	51.1 ± 1.1
25	259 ± 110	513 ± 41

It must be noted that for the equilibrium and rate constants, the errors quoted are rather large; the magnitude of the errors is probably a result of rate measurements being made on reactions that produced only small changes in absorbance. The linear dependence of k_o upon the hydrogen ion concentration was demonstrated at $0^{o}C$; the results are given in table 2.21.

2.3.7. The nitrosation of Mannitol.

The nitrosation of mannitol was studied in aqueous sulphuric acid at $25^{o}C$. Data for the variation of k_o with the mannitol concentration are presented in table 2.22. k_o showed a linear dependence upon the mannitol concentration, the slope and intercept of the graph are given in the table.

The equilibrium constant for the formation of the alkyl nitrite was derived from the experimental data and found to be 2.05 ± 0.07 $l\ mol^{-1}$ at $25^{o}C$. The rate constants k_3 and k_{-2} were calculated to be 709 ± 17 $l^2 mol^{-2} s^{-1}$ and 345 ± 5 $l\ mol^{-1} s^{-1}$ respectively.

The acid catalysis of the reaction was demonstrated

and the results are presented in table 2.23. Again k_o showed a linear dependence upon the hydrogen ion concentration.

2.3.8. The nitrosation of glucose.

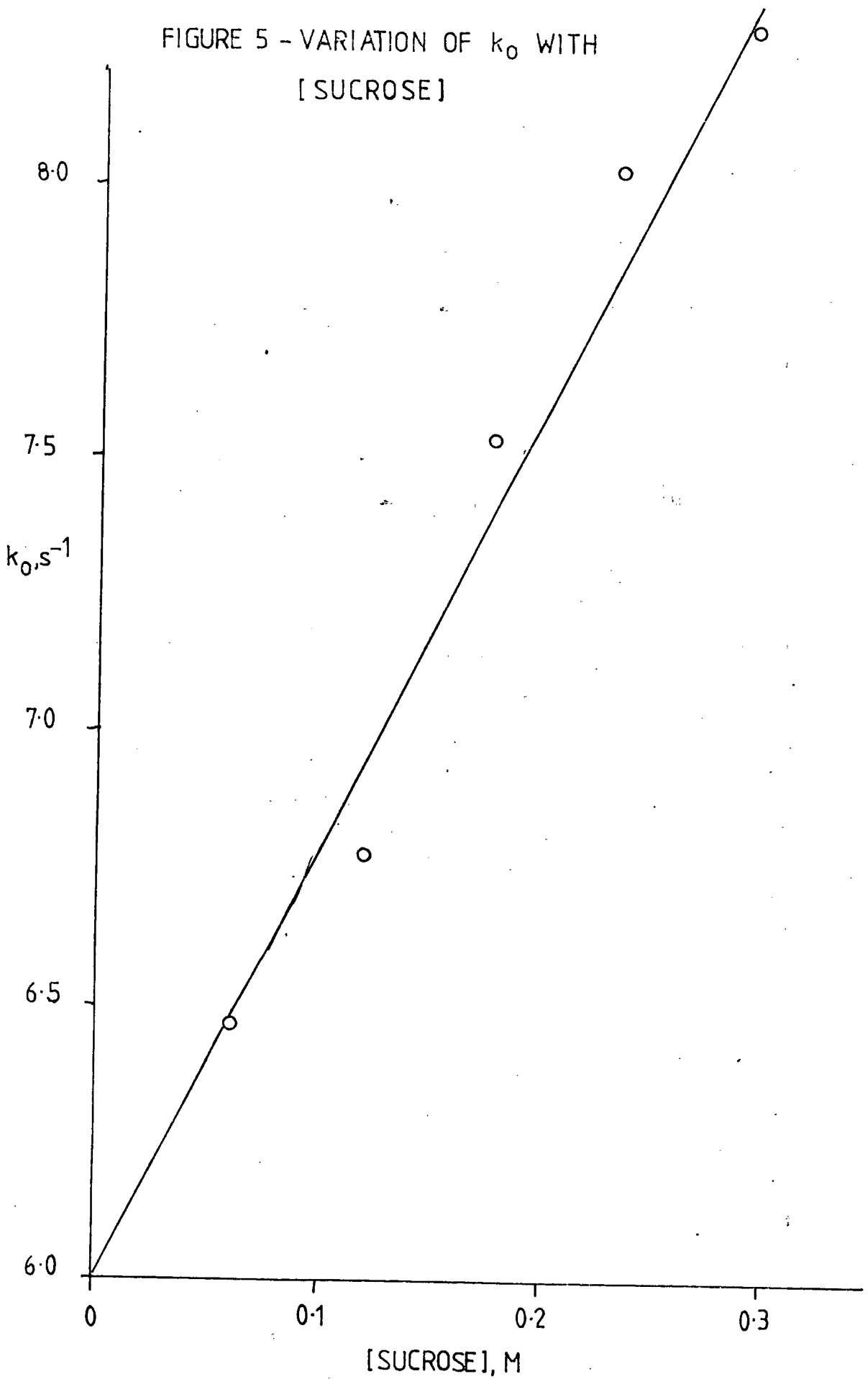
The nitrosation of glucose in aqueous perchloric acid was studied at 0°C. The dependence of the first order rate coefficient k_o upon the glucose concentration was investigated; the results are presented in table 2.24. A graph of k_o against the glucose concentration was plotted and found to be linear with a positive intercept (the slope and intercept are also given in the table).

From the ratio of the slope to the intercept of the graph the equilibrium constant for the formation of the sugar nitrite was determined to be 1.43 ± 0.27 l mol^{-1} at 0°C. The rate constants k_3 and k_{-2} were calculated to be 117 ± 18 $l^2mol^{-2}s^{-1}$ and 82 ± 3 l $mol^{-1}s^{-1}$ respectively.

2.3.9. The nitrosation of sucrose.

The kinetics of the nitrosation of sucrose were studied at 0°C in aqueous perchloric or sulphuric acid. Working under first order conditions k_o was shown to have a linear dependence on both the hydrogen ion and sucrose concentrations. For the dependence of k_o upon the hydrogen ion concentration, kinetic runs were carried out in sulphuric acid. The results are presented in table 2.25. A plot of k_o against the hydrogen ion concentration was linear (and through the origin) indicating a first order

FIGURE 5 - VARIATION OF k_o WITH [SUCROSE]



dependence of k_o upon the acidity. Working in sulphuric acid and following the rather small change in absorbance at 360nm the results obtained for the variation of k_o with the sucrose concentration showed little, if any, trend. However, later results (obtained by following the change in absorbance at 290nm when a deuterium lamp became available and using a lower initial sodium nitrite concentration in aqueous perchloric acid) showed that k_o followed the expected linear dependence on the sucrose concentration (table 2.26) and a graph of k_o against the sucrose concentration (fig. 5) had the slope and intercept given in the table. From the ratio of the slope to the intercept the equilibrium constant for the formation of the alkyl nitrite was calculated to be 1.62 ± 0.16 l mol^{-1}. The rate constant k_3 was found to be 107 ± 14 $l^2 mol^{-2} s^{-1}$ and k_{-2} was calculated to be 66 ± 2 l $mol^{-1} s^{-1}$.

2.3.10. Summary of results and discussion.

The equilibrium constants and rate constants for the nitrosation of the various alcohols and carbohydrates are collected and presented in the table overleaf.

The rate law established for the methanol reaction has been shown to apply to all the other alcohols (and carbohydrates) studied in this project. Therefore, for the nitrosation of an alcohol, ROH, and the reverse reaction (the hydrolysis of the alkyl nitrite) the following rate expressions apply:

$$\text{forward rate} = k_3[ROH][H^+][HNO_2]$$

$$\text{reverse rate} = k_{-2}[RONO][H^+]$$

Rate and equilibrium data for alkyl nitrite equilibria.

ROH	k_3 $l^2 mol^{-2} s^{-1}$	k_{-2} $l\ mol^{-1} s^{-1}$	K $l\ mol^{-1}$	T ^oC
methanol	700± 100	576 ± 57	1.23 ± 0.36	25
	67.3 ± 0.8	34.5 ± 5.7	1.95 ± 0.32	0
ethanol	173 ± 23	298 ± 9	0.58 ± 0.09	25
	37.8 ± 0.3	46.9 ± 0.2	0.81 ± 0.10	0
n-propanol	29.3 ± 1.1	44.1 ± 1.0	0.66 ± 0.04	0
i-propanol	9.83 ± 0.73	43.9 ± 0.5	0.22 ± 0.02	0
t-butanol	-	ca. 103	< 0.1	0
ethanediol	460 ± 20	332 ± 5	1.38 ± 0.08	25
glycerol	259 ± 110	513 ± 41	0.84 ± 0.08	25
	42.7 ± 3.2	51.1 ± 1.1	0.50 ± 0.26	0
mannitol	709 ± 17	345 ± 5	2.05 ± 0.07	25
glucose	117 ± 18	82 ± 3	1.43 ± 0.27	0
sucrose	107 ± 14	66 ± 2	1.62 ± 0.16	0

It is concluded that the reaction mechanism outlined in Scheme 1 is also applicable to the nitrosation of all the substrates studied in this work.

From the table on the previous page the most prominent feature is that for the simple alcohols, that is those containing only one hydroxyl group, the equilibrium constants at $0^{o}C$ show a significant decrease in the sequence:

$$CH_3OH > CH_3CH_2OH > (CH_3)_2CHOH > (CH_3)_3COH$$

The rate constants $\frac{k_{-2}}{k}$ in this series of alcohols are, with the exception of t-butanol, virtually constant. It appears, therefore that the decreases in the values of the equilibrium constants in the above sequence is largely a consequence of decreases in the rate constant k_3 for the forward process. In support of this, the values of k_3 shown in the table do show significant decreases in the same sequence as the decrease in the equilibrium constants.

The rate constant k_3 includes the equilibrium constant for the protonation of the nitrous acid. However, this equilibrium constant will be almost unaffected by the change from one alcohol to another and therefore changes in k_3 upon changing the alcohol are a direct result of changing the nature of the alkyl group. Changes in the nature of the alkyl group may have two effects - electronic or steric.

Considering the electronic effects, going along the series methanol, ethanol, i-propanol and t-butanol, the electron donating effect of the substituents would tend to cause an increase in the rate constant for the nitrosation whereas the values of k_3 were actually seen to decrease.

Therefore, electronic effects cannot be responsible for the changes in k_3. The changes in k_3 must be the result of some other effect - probably steric factors.

Jones and Thomas[107] studied the alkaline hydrolysis of various alkyl acetates in 70% (by volume) aqueous acetone at 24.7°C. For the sequence of methyl, ethyl, i-propyl, t-butyl acetates the rate constants showed significant decreases as shown in the table below. Again, electronic effects did not provide an explanation for the results and it was concluded that steric factors were responsible for the decrease.

Alkaline hydrolysis of alkyl acetates.[107]

R-	10^3 k, l $mol^{-1}s^{-1}$
methyl-	108
ethyl-	46.6
i-propyl-	7.06
t-butyl-	0.265

For the formation of alkyl nitrites, the observed decreases in k_3 in the sequence methyl- to t-butyl nitrite were less marked but it seems that steric effects are most probably the cause of these decreases. For the nitrosation of the various alcohols and sugars at 0°C, the rate constant k_3 ranges over a factor of about ten. In relation to the question of diffusion control in O-nitrosation reactions it is of interest to compare k_3 with the corresponding rate constants for reactions which are regarded as approaching the diffusion controlled limit. On making such a

comparison it becomes apparent that although the O-nitrosation reactions considered in this study are rapid they do not really come under the classification of diffusion controlled reactions.

Schmid and Riedl[83] have determined the equilibrium constants for the formation of alkyl nitrites by an indirect method based upon the nitrosation of phenol. The values of the equilibrium constants derived via this method show the same trends as found in the present work for the series of alcohols- methanol, ethanol, i-propanol, t-butanol. Schmid and Riedl also found that the equilibrium constants for the formation of the butyl nitrites decreased going from primary to secondary to tertiary butanols. They discussed their results in terms of the same type of reaction mechanism as that outlined in Scheme 1. From the experimental data, Schmid and Riedl also calculated rate coefficients for the O-nitrosation of the alcohols and also found that the rate coefficients decreased in the same sequence as the equilibrium constants. Their findings were discussed in terms of increasing steric hinderance of the nitrosyl group from water to the alcohol.

As expected, the mechanism proposed in Scheme 1 and that proposed by Schmid and Riedl are also consistent with the mechanism proposed by Allen for the hydrolysis of alkyl nitrites in aqueous acidified dioxan[73] discussed in Chapter 1.

2.4. The halide ion catalysis of the formation of alkyl nitrites.

Preliminary investigations in this study indicated that small increases in the rate of formation of methyl nitrite were produced by the addition of chloride ions or bromide ions to aqueous solutions of nitrous acid and methanol. The catalysis of the formation of methyl nitrite was, therefore the subject of further investigation and the study was also extended to a secondary alcohol (i-propanol).

2.4.1. The chloride ion catalysed formation of methyl nitrite.

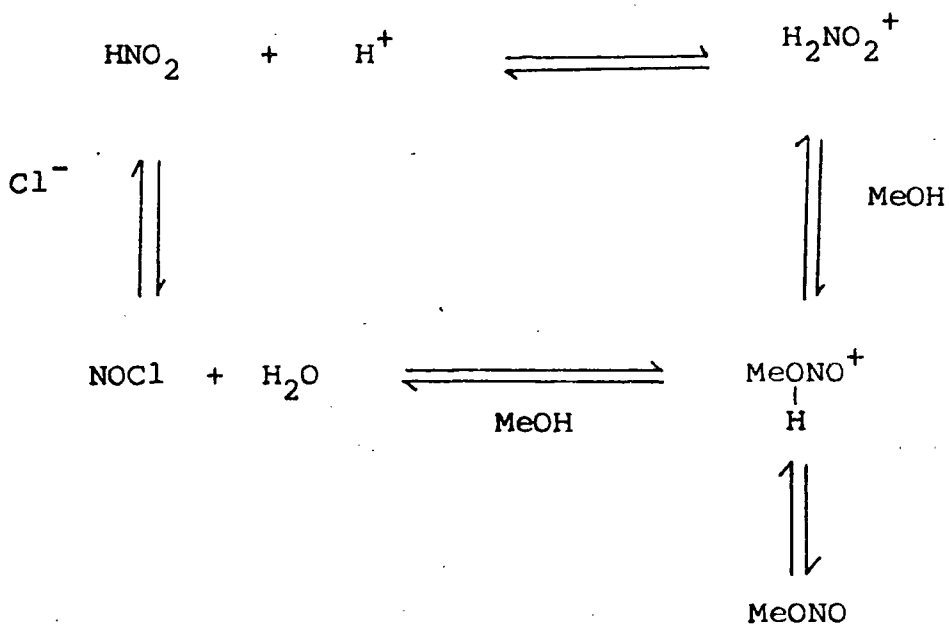
Kinetic runs were carried out in the presence of a large excess of methanol. Rate measurements were made at $0^{o}C$ and $25^{o}C$.

NITROSATION OF METHANOL AT $25^{o}C$

The variation of the first order rate coefficient, k_o, with the methanol and chloride ion concentration was investigated and the results are presented in table 2.27. The results demonstrated that k_o showed a linear dependence upon the concentrations of both methanol and chloride ions. For the dependence of k_o upon the chloride ion concentration at each methanol concentration the best slopes and intercepts are quoted in table 2.28. The catalysis of both the forward and reverse reactions by chloride ions and hydrogen ions would be expected if the nitrosation of methanol were occurring via nitrosyl chloride and the denitrosation of the methyl nitrite were occurring via the denitrosation of

the protonated form of methyl nitrite involving chloride ion as the nucleophile. Thus on the basis of this mechanism (outlined in Scheme 2) the expression for the experimentally determined first order rate coefficient would be modified to equation 2.9.

$$k_0 = k_3[H^+][MeOH] + k_{Cl^-}[H^+][MeOH][Cl^-] + k_{-2}[H^+] + k_{Cl^-}[H^+][Cl^-] \qquad 2.9$$



Scheme 2

From equation 2.9 it is indicated that the rate constants k_{Cl^-} and k_{-Cl^-} could be obtained via a graph of the slopes of the graphs of k_o against the chloride ion concentration against the methanol concentration. From this graph k_{Cl^-} was obtained from the slope and k_{-Cl^-} from the intercept. The slope and intercept of the best straight line were calculated to be

$$\text{slope} = 11.4 \pm 1.0\ l^2 mol^{-2} s^{-1}$$

$$\text{intercept} = 49.5 \pm 0.4\ l\ mol^{-1} s^{-1}$$

Dividing the slope by the hydrogen ion concentration gave the value of k_{Cl^-} to be $219 \pm 20\ l^3 mol^{-3} s^{-1}$ at 25°C;

the value of k_{Cl^-} to be 219 ± 20 $l^3mol^{-3}s^{-1}$ at 25°C; similarly the rate constant k_{-Cl^-} was calculated to be 951 ± 86 $l^2mol^{-2}s^{-1}$ from the intercept of the graph.

Upon the addition of chloride ions to an aqueous solution of nitrous acid, the equilibrium constant between nitrous acid and the nitrosyl chloride is established (equation 2.10). The magnitude of the equilibrium constant

$$HNO_2 + H_3O^+ + Cl^- \rightleftharpoons NOCl + 2H_2O \qquad 2.10$$

K_{NOCl}, has been determined[99,108] and at 25°C has the value of 1.136×10^{-3} l^2mol^{-2}.

For the direct reaction between nitrosyl chloride and methanol:

$$NOCl + CH_3OH \xrightarrow[(H_2O)]{k_4} CH_3ONO + H_3O^+ + Cl^-$$

the rate expression in equation 2.11 applies.

$$\text{rate} = k_{NOCl}[NOCl][CH_3OH] \qquad 2.11$$

The rate of reaction may also be expressed in terms of the equilibrium constant, K_{NOCl}, rather than in terms of the nitrosyl chloride concentration (equation 2.12).

$$\text{rate} = k_{NOCl}K_{NOCl}[HNO_2][H^+][Cl^-][CH_3OH] \qquad 2.12$$

However, the present study has established the rate equation given in equation 2.13 as the rate expression for the forward reaction:

$$\text{rate} = k_{Cl^-}[HNO_2][Cl^-][CH_3OH] \qquad 2.13$$

Thus from the experimental data, k_{NOCl} may be evaluated from the relationship:

$$k_{NOCl} = \frac{k_{Cl^-}}{K_{NOCl}[H^+]}$$

and was determined to be $(1.93 \pm 0.17) \times 10^5$ l $mol^{-1}s^{-1}$.

THE NITROSATION OF METHANOL AT 0°C.

Working at 0°C the dependence of k_o upon the methanol concentration was studied in the absence of halide ions and then in the presence of chloride ions (ca. 0.5M). The results are given in tables 2.29, 2.30, 2.31, and 2.32. Using the data in these tables and the expression for the first order rate constant (equation 2.9) the rate constants k_{Cl^-} and k_{-Cl^-} were calculated to be

$$k_{Cl^-} = 28 \pm 14 \text{ l}^3\text{mol}^{-3}\text{s}^{-1}$$

$$k_{-Cl^-} = 56 \pm 18 \text{ l}^2\text{mol}^{-2}\text{s}^{-1}$$

Using the value for the equilibrium constant for the formation of nitrosyl chloride from nitrous acid at 0°C determined by Schmid and Hallaba as 5.5×10^{-4} l^2mol^{-2},[27], the rate constant k_{NOCl} for the nitrosation of methanol by nitrosyl chloride as $(5.1 \pm 3.6) \times 10^4$ l $mol^{-1}s^{-1}$.

2.4.2. The bromide ion catalysed formation of methyl nitrite.

AT 25°C.

The formation of methyl nitrite from nitrous acid and methanol in aqueous sulphuric acid was also found to be subject to bromide ion catalysis. The results for the variation of k_o with the concentration of each reagent are given in tables 2.33, 2.34, 2.35, and 2.36. Linear relationships between k_o and the concentrations of methanol, hydrogen ions and bromide ions were established.

The rate constants k_{Br^-} and k_{-Br^-} were determined by means of plotting graphs of k_o against the bromide ion concentration for each methanol concentration and each acidity. The best slopes of these graphs were then plotted against the acidity for each methanol concentration. Finally a plot of the slopes of these graphs against the methanol concentration yielded the values of k_{Br^-} and k_{-Br^-}. The rate constants k_3 and k_{-2} were also obtained by treating the intercepts of the k_o against [bromide ion] graphs in exactly the same manner. Details of the graphs are given in tables 2.37, 2.38 and 2.39.

The rate constants k_{Br^-}, k_{-Br^-}, k_3 and k_{-2} were found to have the following values:

$$k_3 = 879 \pm 114 \ l^2 mol^{-2} s^{-1}$$

$$k_{-2} = 225 \pm 38 \ l \ mol^{-1} s^{-1}$$

$$k_{Br^-} = 1003 \pm 91 \ l^3 mol^{-3} s^{-1}$$

$$k_{-Br^-} = 1047 \pm 33 \ l^2 mol^{-2} s^{-1}$$

The rate constant k_{Br^-} determined above includes the equilibrium constant for the formation of nitrosyl bromide. For the reaction between nitrosyl bromide and methanol:

$$NOBr + CH_3OH \xrightarrow{k_{NOBr}} CH_3ONO + H_3O^+ + Br^-$$

the rate of reaction is given by equation 2.14. The rate

$$\text{rate} = k_{NOBr}[NOBr][MeOH] \qquad 2.14$$

may be also be expressed in terms of the equilibrium constant, K_{NOBr}, and the nitrous acid concentration (equation 2.15)

$$\text{rate} = k_{NOBr} K_{NOBr} [HNO_2][H^+][Br^-][MeOH] \qquad 2.15$$

The rate constant refers to the rate expression given in equation 2.16 and the relationship between k_{Br^-} and k_{NOBr}

$$\text{rate} = k_{Br^-}[HNO_2][H^+][Br^-][MeOH] \qquad 2.16$$

may be seen in equation 2.17

$$k_{NOBr} = \frac{k_{Br^-}}{K_{NOBr}} \qquad 2.17$$

The equilibrium constant, K_{NOBr}, has been evaluated at 25°C in aqueous solution[99] to be 5.1×10^{-2} $l^2 mol^{-2}$. Using this value of K_{NOBr}, the rate constant k_{NOBr} was calculated to be $(1.97 \pm 0.18) \times 10^4$ $l\ mol^{-1} s^{-1}$.

AT 0°C.

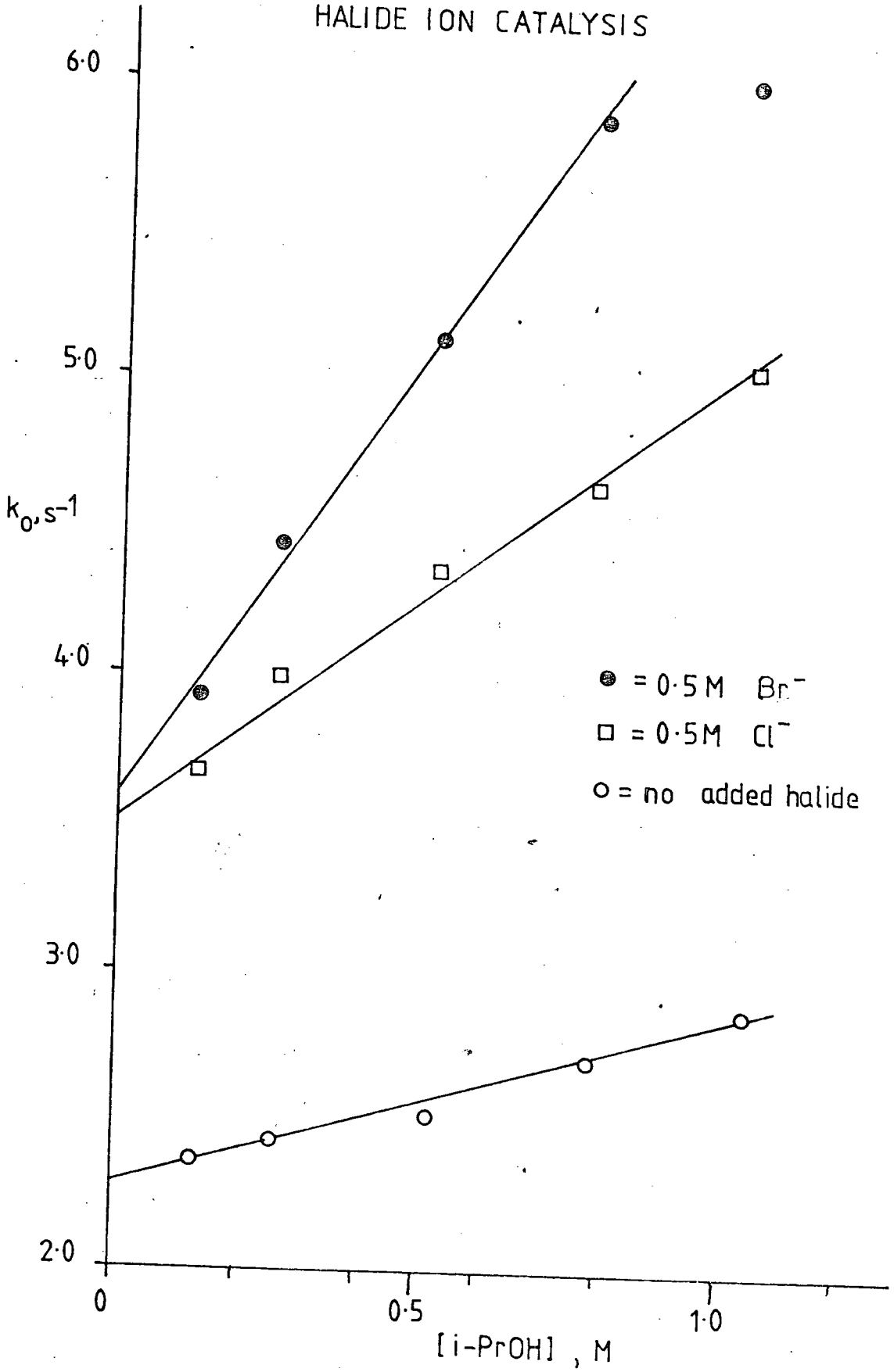
The variation of the first order rate constant, k_o, with the methanol concentration was investigated and the results are presented in table 2.40 and are illustrated, together with the data for runs in the presence of chloride ions and in the absence of halide ions in figure 6. Using these data and the data in table 2.29(for the variation of k_o in the absence of halide ions) the rate constant k_{Br^-} was determined from the slope of the graph of k_o against the methanol concentration using the relationship in equation 2.18. Similarly, the intercept of the same graph would

$$\text{slope} = k_3[H^+] + k_{Br^-}[H^+][Br^-] \qquad 2.18$$

yield the value of k_{-Br^-} for the reaction between the protonated methyl nitrite and the bromide ion (equation 2.19). The values of the rate constants k_3 and k_{-2} were calculated

$$\text{intercept} = k_{-2}[H^+] + k_{-Br^-}[H^+][Br^-] \qquad 2.19$$

FIGURE 6 - NITROSATION OF i-PROPANOL, HALIDE ION CATALYSIS



from the variation of k_o with the methanol concentration in the absence of bromide ions. The rate constants k_{Br^-} and k_{-Br^-} were found to have the values:

$$k_{Br^-} = 80 \pm 20 \quad l^3 mol^{-3} s^{-1}$$

$$k_{-Br^-} = 69 \pm 3 \quad l^2 mol^{-2} s^{-1}$$

The rate constant for the nitrosation of methanol by nitrosyl bromide, k_{Br^-}, contains the equilibrium constant, K_{NOBr}, for the formation of nitrosyl bromide. At 0°C K_{NOBr} has been shown to be 2.2×10^{-2} $l^2 mol^{-2}$.[99] Using this value, the true rate constant for the nitrosation of methanol by nitrosyl bromide, k_{NOBr}, was calculated to be $(3.6 \pm 1.3) \times 10^3$ $l\ mol^{-1} s^{-1}$.

2.4.3. The halide ion catalysed nitrosation of i-propanol.

The catalysis of the nitrosation of i-propanol by bromide ions and chloride ions was carried out in order to make a comparison between the halide ion catalysed nitrosation of a primary and a secondary alcohol. Reactions were carried out at 0°C under first order conditions using a large excess of the alcohol. The dependence of the first order rate coefficient k_o on the i-propanol concentration in aqueous sulphuric acid containing no added halide ions was compared with results obtained using solutions containing added chloride ions or added bromide ions. The results are presented in tables 2.41 to 2.46 (the set of reactions was carried out in duplicate). In all cases, graphs of k_o against the i-propanol concentration proved to be

reasonable straight lines (fig. 6 shows one set of results), the slopes and intercepts being given in the appropriate tables.

For the reaction in the absence of added halide ions the rate constants for the forward and reverse reactions were calculated from the slope and intercept respectively and were shown to have the following values:

$$k_3 = 13.2 \pm 3.7 \ l^2 mol^{-2} s^{-1}$$

$$k_{-2} = 45.7 \pm 2.1 \ l \ mol^{-1} s^{-1}$$

From the two sets of data the equilibrium constant for the formation of i-propyl nitrite at $0^{\circ}C$ was calculated to be $0.30 \pm 0.03 \ l \ mol^{-1}$.

For the reaction in the presence of chloride ions the rate constant k_{Cl^-} was calculated from the slope of the graph of k_o against the i-propanol concentration, using the previously determined value of k_3 for the acid catalysed reaction. Likewise, k_{-Cl^-} was determined from the intercept of the same graph via the value of k_{-2} determined from the series of kinetic runs made in the absence of added halide ions. k_{Cl^-} and k_{-Cl^-} were found to have the following values:

$$k_{Cl^-} = 36 \pm 10 \ l^3 mol^{-3} s^{-1}$$

$$k_{-Cl^-} = 30 \pm 30 \ l^2 mol^{-2} s^{-1}$$

For the reaction in the presence of bromide ions, the data were treated in exactly the same way as before and the calculated values of the rate constants k_{Br^-} and k_{-Br^-} were:

$$k_{Br^-} = 64 \pm 37 \ l^3 mol^{-3} s^{-1}$$

$$k_{-Br^-} = 53 \pm 3 \ l^2 mol^{-2} s^{-1}$$

Using the values of the equilibrium constants for the formation of the nitrosyl halides determined by Schmid and co-workers (5.5×10^{-4} $l^2 mol^{-2}$ and 2.2×10^{-2} $l^2 mol^{-2}$ at 0^oC for nitrosyl chloride and nitrosyl bromide respectively) and the rate constants for the reaction between i-propanol and the nitrosyl halide were calculated as

$$k_{NOCl} = (6.5 \pm 1.8) \times 10^4 \text{ l mol}^{-1}\text{s}^{-1}$$
$$k_{NOBr} = (2.9 \pm 1.7) \times 10^3 \text{ l mol}^{-1}\text{s}^{-1}.$$

2.4.4. The halide ion catalysed reaction; summary and discussion.

In the table below the values of the true rate constants, k_{NOX}, at 0^oC for the nitrosation of methanol and i-propanol by nitrosyl chloride and nitrosyl bromide are shown:

	k_{NOX} values at 0^oC	
X=	k_{NOX}(methanol) $l\ mol^{-1}s^{-1}$	k_{NOX}(i-propanol) $l\ mol^{-1}s^{-1}$
Cl^-	$(5.00 \pm 3.6)\times10^4$	$(6.5 \pm 1.8)\times10^4$
Br^-	$(3.6 \pm 1.3)\times10^3$	$(2.9 \pm 1.7)\times10^3$

Two points are noticed; firstly that for a given alcohol, the value of k_{NOX} is larger, by a factor of ten or more, for the nitrosyl chloride reaction. Secondly, for a given nitrosyl halide there is little difference in the rate constants in going from the reaction with methanol to

i-propanol.

That the rate constant for the nitrosation of an alcohol is larger for the reaction in which the nitrosating agent is nitrosyl chloride is quite readily rationalised. The nitrosation of alcohols involves the electrophilic attack by the nitrosyl halide. On considering nitrosyl chloride and nitrosyl bromide the nitrosyl-halogen bond will be more polarised in the nitrosyl chloride on account of the greater electronegativity of chlorine. The result of this increased polarity would be that nitrosyl chloride would be more electrophilic than nitrosyl bromide.

The catalysis of nitrosation of alcohols was, however, greater when the catalyst was bromide ion. These observationsare completely accounted for when the relative magnitudes of the equilibrium constants for the formation of the nitrosyl halides are considered. K_{NOX} is much larger for the nitrosyl bromide; so much larger that although the nitrosyl bromidereaction does not have as large a rate constant for the nitrosation of an alcohol as the nitrosyl chloride reaction the catalysis is more pronounced. The same observations and conclusions have been made upon other reactions involving nitrosyl halides as nitrosating agents, in particular, the diazotisation of anilines by nitrosyl halides[31].

It would have been of interest to study the catalytic activity of other nucleophiles, in particular thiocyanate ion and thiourea - two nucleophiles which have been demonstrated to be excellent catalysts in N-nitrosation reactions[35]. However, in the study of the nitrosation of

alcohols it was not possible to adjust the reaction conditions for reactions in the presence of thiocyanate ion or thiourea such that the extensive side reactions were sufficiently suppressed to enable rate measurements to be made. The catalysis of the reaction by iodide ion could not be studied for the same reason.

The results of the present study showed that for a given nucleophile there appeared to be little difference between the rate constants, k_{NOX}, for the nitrosation of a primary or a secondary alcohol. This result indicates that for the nitrosation of the alcohol the increased steric effect of replacing the methyl group of the methanol by the i-propyl group of i-propanol does not have a very important effect on the rate of reaction. The effect on the nitrosyl halide reaction is a little different to the reaction involving the nitrous acidium ion; in the latter case steric effects were rather more marked.

The values of k_{NOCl} may be compared to other true rate constants for the nitrosation of other species, for example, the diazotisation of anilines and other N-nitrosation reactions. Values of the rate constants for these reactions are given in the table overleaf. For reaction upon encounter, the rate constant, k_{en}, in water at 25°C has been calculated to be ca. 7.4×10^9 l $mol^{-1}s^{-1}$. The value of the rate constant for the O-nitrosation of methanol by nitrosyl chloride is well below this value and so it is reasonable to conclude that the reaction is not subject to diffusion control. This conclusion is supported by the estimated activation energy for the reaction. From

the values of k_{NOCl} determined at 0° and 25°C the activation energy was estimated to be ca. 35 kJ mol^{-1}. For diffusion controlled reactions the activation energy is typically less than ca. 20 kJ mol^{-1}. In the table below it can be seen that the more reactive substrates have rate constants for their reaction with nitrosyl chloride that are approaching the diffusion controlled limit. From the table, the reactivity of methanol is comparable to, but a little lower than that of the hydrazinium ion.

Rate constants for nitrosation by NOCl in aqueous solution.

substrate	$k \times 10^{-9}$ $l\ mol^{-1}s^{-1}$	T°C	ref.
p-methylaniline	3.00, 4.09	25	32,99
aniline	2.60, 2.15	25	32,99
m-chloroaniline	1.63	25	32
p-nitroaniline	o.21	25	99
ammonia	0.05	25	108
glycine	0.017	25	108
hydroxylamine	0.035	0	47
hydrazinium ion	0.00075	0	109
methanol	0.00019	25	-
	0.00005	0	-

Once again, it is not possible to determine the value of the true rate constant for the denitrosation of the protonated methyl nitrite involving the chloride ion as the

nucleophile because the pK_a of methyl nitrite is not known. However the third order rate constants (which include K_a) for the denitrosation reaction are much larger than those obtained for the denitrosation of N-nitrosamines by chloride ion and it is suggested that the true rate constant for the attack by the chloride ion upon the protonated methyl nitrite is much greater than for the attack upon a protonated nitrosamine.

For the nitrosation by nitrosyl bromide the rate constants k_{NOBr} for various reactions are given in the table below. The reactivity of the alcohols towards nitrosyl bromide lies somewhere between that of the hydroxylamine and the hydrazinium ion. It is interesting to note that there is a difference here in the order of reactivity compared to the nitrosyl chloride reaction.

rate constants for nitrosation by NOBr.

substrate	$k \times 10^9$ $l\ mol^{-1}s^{-1}$	T^oC	ref.
aniline	1.69	25	32
hydroxylamine	0.037	0	47
p-nitroaniline	0.043	25	32
hydrazinium ion	0.0000019	0	109
methanol	0.0000197	25	-

From the values of k_{NOBr} determined at 25°C and 0°C the activation energy for the reaction between nitrosyl bromide and methanol was estimated to be ca. 44 kJ mol^{-1}. As in the

case of the nitrosyl chloride reaction the magnitude of the rate constants and the activation energy for the nitrosyl bromide reaction lead one to conclude that the reaction is not subject to diffusion control.

In his study of the hydrolysis of some alkyl nitrites, Allen demonstrated the catalytic effect of both chloride ion and bromide ion[73]. He reported that at 0°C in 72.5% dioxan-water the third order rate constants, k_3, for the halide ion catalysed reaction (defined inequation 2.20) were 39 $l^2mol^{-2}s^{-1}$ and 27 $l^2mol^{-2}s^{-1}$ for the chloride ion and bromide ion reactions respectively.

$$-\frac{d[RONO]}{dt} = k_2[H^+][RONO] + k_3[H^+][Cl^-][RONO] \qquad 2.20$$

The rate constant k_3 also includes the equilibrium constant for the protonation of the n-propyl nitrite, but since this is going to be the same for both the reaction in the presence of chloride ion and bromide ion, the rate constants for both reactions may be compared. It is immediately noticed that k_3 is larger for the chloride ion reaction than for the reaction in the presence of bromide ion. Both reactions involve nucleophilic attack on the protonated alkyl nitrite. So there is the rather unusual result that the chloride ion appears to be behaving as a more efficient nucleophile than bromide ion. Allen's rate constants are analogous to the rate constants k_{-X^-} determined in the present study. The values of k_{-X^-} for the two alcohols are shown in the table overleaf.

rate constants for the hydrolysis of alkyl nitrites at $0^{o}C$

	methyl nitrite	i-propyl nitrite
k_{-Cl}- $l^2mol^{-2}s^{-1}$	55 ±17	30 ±30
k_{-Br}- $l^2mol^{-2}s^{-1}$	69 ± 4	52 ± 4

The rate constants in the table are all very similar. The reaction involves the nucleophilic attack of the halide ion upon the protonated alkyl nitrite and the fact that there is little difference in reactivity between the two nucleophiles indicates that the hydrolysis of the alkyl nitrite could be subject to diffusion control or at least is approaching such a limit.

2.5. Experimental details.

2.5.1. Reagents.

a)alcohols and sugars. The alcohols used were all of the highest purity that was available; normally this meant that they were of analytical grade but in the case of t-butanol standard laboratory grade was used and the alcohol was fractionally distilled, the middle fraction being used. For the sugars, the highest grade available was also used without further purification.

b)inorganic reagents. Perchloric acid solutions were prepared by diluting appropriate volumes of 60-62% perchloric acid with distilled water. Sulphuric acid solutions were prepared by diluting 98% analytical grade concentrated sulphuric acid. Acid solutions were standardised by titration against standard sodium hydroxide solutions using phenol red as the indicator of the end-point. For the sulphuric acid solutions the hydrogen ion concentrations were calculated by means of the data of Robertson and Dunford[110].

Analytical grade potassium bromide, potassium chloride, sodium bromide and sodium chloride were used. The sodium nitrite used was normally of analytical grade but when this was not available S.L.R. grade sodium nitrite was used.

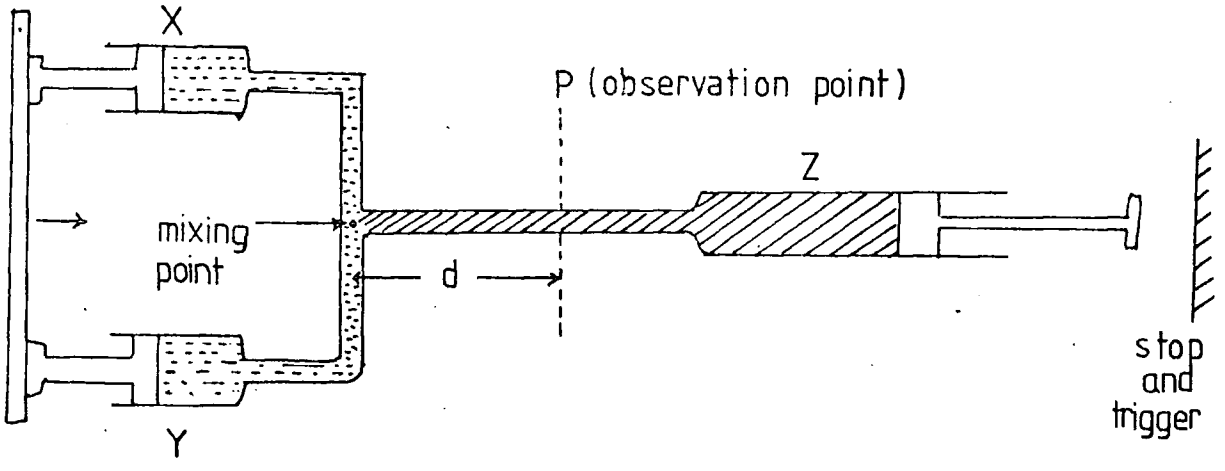
2.5.2. A brief description of the principles of the stopped-flow technique.

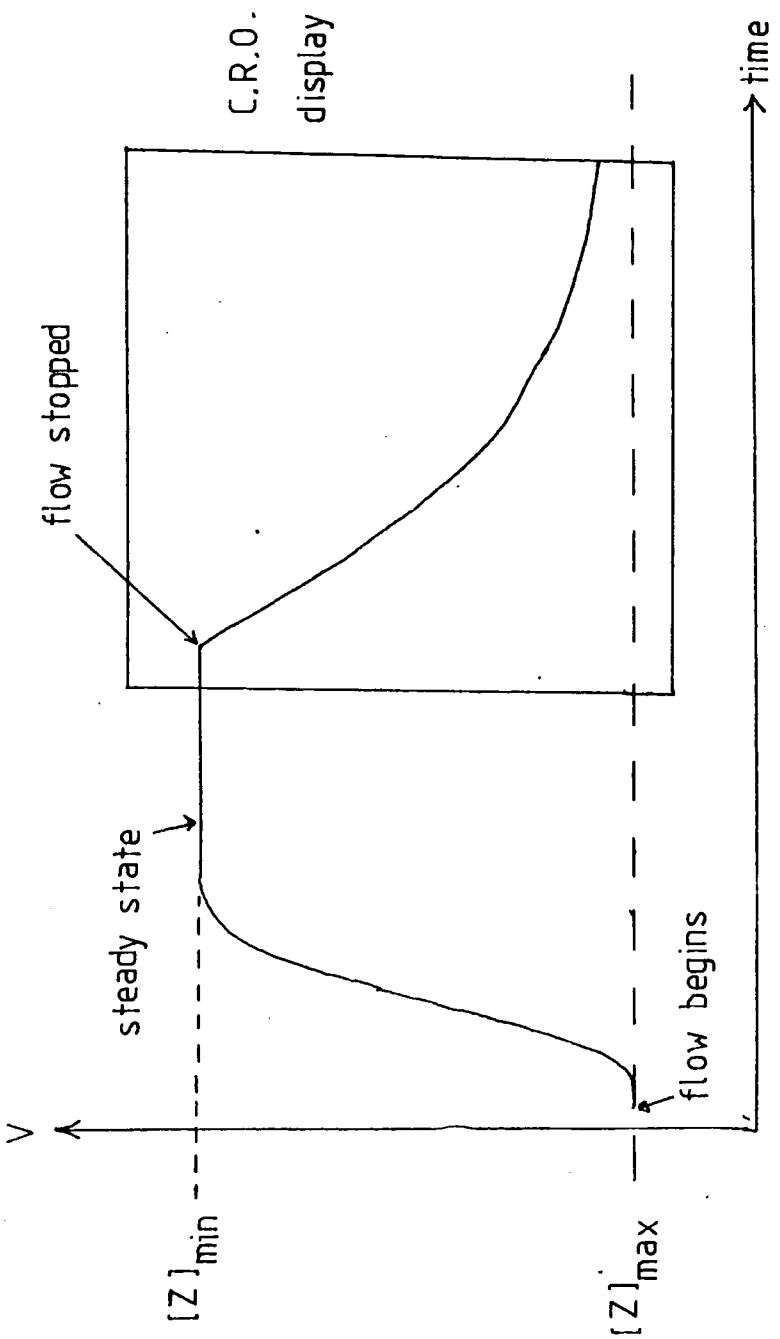
Stopped-flow spectrophotometry is an experimental method which allows kinetic measurements to be made on reactions resulting from the mixing of two solutions X and Y in the

cell of the spectrophotometer. Before mixing, the two solutions are stored in two identical syringes. The syringes have a shared piston mechanism and therefore samples leaving each syringe have the same flow rates (provided that the syringes are identical). The solutions pass through thermostatting coils and then into the cell of the spectrophotometer where upon mixing the following reaction occurs:

$$X + Y \longrightarrow Z$$

After mixing the reacting solution leaves the cell and passes into a third syringe. The piston of this syringe is pushed back and hits a stop; the flow is then stopped and the recording instrument is triggered at the same time (in the case of the Canterbury stopped-flow instrument the recording instrument is an oscilloscope). A beam of monochromatic light passes through the solution at the observation point P and its intensity is converted into an electrical signal (which, under certain conditions is proportional to the light intensity) and is displayed upon the C.R.O. screen.




C.R.O.
display
flow stopped
steady state
flow begins
V
time
$[Z]_{min}$
$[Z]_{max}$

If the sequence of stages in the process are considered at point P (which is distance, d, from the mixing point in the direction of the flow), before the flow is started the apparatus is filled with solutions X or Y as far as the mixing point and with Z beyond the mixing point (see the figure on the previous page). When the reactant solutions are pushed through the mixing point, a steady state is reached at each point beyond the mixing point (including point P) characterised by the fraction of the reaction that had already taken place in the time defined by the distance from the mixing point (e.g. distance, d, for point P) and the linear flow rate in the system. On stopping the flow suddenly the steady state solution is stopped at point P and the reaction continues at point P. Considering the concentration of the product, [Z], the concentration of Z would be at a maximum before the flow is started ($[Z]_{max}$) and then reaches a minimum value ($[Z]_{min}$, which would be zero if the distance of the observation point from the mixing point were zero) when the steady state is reached. The steady state concentration would be maintained as long as the solutions were flowing but upon halting the flow the reaction proceeds from $[Z]_{min}$ to $[Z]_{max}$ and so the reaction may be monitored (see the figure overleaf).

The cell of the stopped-flow spectrophotometer is submerged in a thermostat bath; kinetic measurements were made at $0^{o}C$ or $25^{o}C$. Three different Canterbury stopped-flow instruments were used, the models SF-3A and SF-3L at Durham University and the model SF-3C in the chemistry department at the University College of Swansea.

2.5.3. Kinetic measurements.

In order to observe the formation of the alkyl nitrites by the stopped-flow technique two solutions were prepared; one containing the sodium nitrite, the other containing all other reagents (the alcohol, an acid and, if required, halide salts). Upon mixing the two solutions, the nitrosating agent would be formed rapidly and would then react with the alcohol to form the alkyl nitrite.

The reactions were monitored by recording the increase in absorbance due to the formation of the alkyl nitrite (except in the case of methyl nitrite; its formation from nitrous acid results in a decrease in absorbance at 386nm) at any suitable wavelength. The actual wavelengths used are given in the table below:

Wavelengths for following alkyl nitrite formation.

alcohol.	wavelength,nm.
methanol	384,386
ethanol	370,290
n-propanol	285
i-propanol	285
t-butanol	290
ethanediol	360
glycerol	360
mannitol	360
glucose	290
sucrose	360,290

Kinetic runs were carried out by mixing equal volumes of the two solutions so that upon mixing the concentrations of all the species in the two solutions were exactly halved,

provided the syringes had been properly flushed before taking kinetic measurements. In all cases, reactions were carried out under first order conditions with the alcohol present inlarge excess over the sodium nitrite.

Duplicate kinetic runs generally did not give as good agreement as hoped. Therefore, in order to obtain meaningful values of the first order observed rate constant, k_o, kinetic runs were repeated at least five times and the mean value of the rate coefficients taken as k_o. The first order rate coefficients k_o were calculated from the slope of a plot of $\ln(V_t - V_\infty)$ or $\ln(V_\infty - V_t)$ against time, where V is the voltage of the output signal and,under the experimental conditions used here, is proportional to the absorbance. The tables overleaf show a typical kinetic run and a typical set of rate constants, k_o, obtained from a series of duplicate kinetic runs. The instantaneous rate coefficients given in the table were calculated via equation 2.21.

$$k_o = \frac{1}{t} \ln \frac{(V_o - V_\infty)}{(V_t - V_\infty)} \qquad 2.21$$

The slopes and intercepts of all linear correlations were calculated via the principle of least squares.

A typical kinetic run.

the bromide ion catalysed nitrosation of methanol.

$[MeOH] = 0.741$ M
$[H^+] = 0.052$ M
$[Br^-] = 0.5$ M
$[NaNO_2] = 0.01$ M

t, ms	V_t, mV	k_o, s^{-1}
0	84	-
20	114	6.80
40	140	6.77
60	164	6.90
80	190	7.45
100	208	7.45
120	212	6.51
140	238	7.55
160	250	7.60
∞	320	-

$k_o = 7.13\ s^{-1}$

A typical set of duplicate runs.

(the concentrations of reagents are the same as given in the table above)

run	k_o, s^{-1}
1	7.48
2	7.97
3	7.60
4	7.97
5	7.25

2,6 Tables of Results.

Table 2.1

($[H^+]$ = 0.069M, $[NaNO_2]$ = 0.04M)

[MeOH],M	k_o, s^{-1}
0.198	38.2 ± 1.3
0.395	44.9 ± 2.1
0.494	47.5 ± 3.0
0.593	48.2 ± 3.3
0.741	50.8 ± 2.6
0.890	54.7 ± 3.4
0.988	55.7 ± 3.9
1.234	66.5 ± 3.0
1.481	63.7 ± 2.0

Table 2.2

($[H^+]$ = 0.1035M, $[NaNO_2]$ = 0.04M)

[MeOH],M	k_o, s^{-1}
0.198	58.2 ± 5.2
0.395	72.5 ± 3.2
0.494	80.0 ± 4.4
0.593	87.0 ±1.1
0.741	97.1 ± 10.6
0.890	98.1 ± 1.6
0.988	98.6 ± 2.7
1.234	107 ± 4
1.481	114 ± 4

Table 2.3

($[H^+]$ = 0.138M, $[NaNO_2]$ = 0.04M)

[MeOH],M	k_o, s^{-1}
0.198	86.2 ± 2.1
0.395	109.5 ± 1.7
0.494	109.2 ± 6.0
0.593	132.4 ± 5.4
0.741	133.7 ± 3.7
0.890	152.1 ± 11.0
0.988	156.3 ± 14.5
1.234	163.7 ± 2.7
1.481	164.6 ± 8.8

Table 2.4

($[H^+]$ = 0.1725M, $[NaNO_2]$ = 0.04M)

[MeOH],M	k_o, s^{-1}
0.198	123.0 ± 13.0
0.395	150.9 ± 4.6
0.494	162.2 ± 16.6
0.593	169.8 ± 6.5
0.741	189.7 ± 9.0
0.890	194.9 ± 5.2
0.988	204.3 ± 9.1
1.234	219.7 ± 14.9
1.481	228.4 ± 1.7

Table 2.5 catalysis by perchloric acid.

($[NaNO_2]$ = 0.04M, [MeOH] = 0.493M)

$[H^+]_{xs} \times 10^2$, M	k_o, s^{-1}
0.511	5.18 ± 0.35
2.015	13.3 ± 0.4
3.52	24.8 ± 0.8
5.02	33.4 ± 1.0
8.03	55.2 ± 3.2

slope = 66.9 ± 1.9 l $mol^{-1}s^{-1}$

Table 2.6 catalysis by sulphuric acid.

($[NaNO_2]$ = 0.04M, [MeOH] = 0.493M)

$[H^+]_{xs} \times 10^2$, M	k_o, s^{-1}
0.70	14.7 ± 0.6
1.80	22.9 ± 1.0
2.90	28.6 ± 0.7
5.30	45.1 ± 1.0
7.80	59.0 ± 2.9

slope = 62.4 ± 1.6 l $mol^{-1}s^{-1}$

Table 2.7 variation of k_o with the nitrite concentration.

([MeOH] = 1.91M, $[H_2SO_4]$ = 0.172M)

$[NaNO_2] \times 10^2$, M	k_o, s^{-1}	"k_1, s^{-1}
2.01	109	109
4.04	84.0	93
5.85	72.4	92
7.25	62.7	86

Table 2.8 dependence of k_o on [methanol] at 0°C

($[NaNO_2]$ = 0.04M, $[H^+]_{xs}$ = 0.054M)

[MeOH],M	k_o, s^{-1}
0.123	2.18 ± 0.03
0.247	2.75 ± 0.14
0.370	3.34 ± 0.12
0.494	3.62 ± 0.13
0.615	3.95 ± 0.13

slope = 3.58 ± 0.33 l $mol^{-1}s^{-1}$
intercept = 1.84 ± 0.14 s^{-1}

Table 2.9 dependence of k_o on acidity at 0°C

($[NaNO_2]$ = 0.04M, [MeOH] = 0.494M)

$[H^+]_{xs}$ x 10^2,M	k_o,s^{-1}
0.51	0.44 ± 0.03
2.02	1.33 ± 0.11
3.52	2.21 ± 0.04
5.02	3.44 ± 0.16
8.03	5.48 ± 0.13

slope = 67.8 ± 2.2 l $mol^{-1}s^{-1}$

Table 2.10 dependence of k_o on [ethanol] at 25°C
([H^+] = 0.066M, [$NaNO_2$] = 0.04M)

[EtOH],M	k_o, s^{-1}
0.129	20.7 ± 2.2
0.257	23.3 ± 1.7
0.376	24.0 ± 0.5
0.514	27.1 ± 0.9
0.642	26.9 ± 1.3

slope = 11.45 ± 1.54 l $mol^{-1}s^{-1}$
intercept = 19.70 ± 0.62 s^{-1}

Table 2.11 formation of ethyl nitrite; acid catalysis.

([EtOH] = 0.257M, [$NaNO_2$] = 0.04M)

$[H_2SO_4]_{added}$ x 10^2,M	$[H^+]_{xs}$ x 10^2,M	k_o,s^{-1}
3.75	4.9	15.2 ± 0.6
5.00	6.6	35.6 ± 8.0
7.75	10.2	48.0 ± 4.0
10.0	13.2	60.0 ± 4.0
12.5	16.5	74.8 ± 9.5

slope = 472 ± 55 l $mol^{-1}s^{-1}$

Table 2.12 dependence of k_o upon [ethanol] at 0°C

($[NaNO_2]$ = 0.0103M, $[H^+]_{xs}$ = 0.0845M)

[EtOH],M	k_o,s^{-1}
0.171	4.51 ± 0.11
0.343	5.07 ± 0.09
0.514	5.61 ± 0.12
0.686	6.13 ± 0.11
1.029	7.26 ± 0.12

slope = 3.19 ± 0.03 l $mol^{-1}s^{-1}$
intercept = 3.96 ± 0.02 s^{-1}

Table 2.13 dependence of k_o upon [n-propanol].

($[NaNO_2]$ = 2.5 x 10^{-3}M, $[H^+]_{xs}$ = 0.0923M)

[n-PrOH],M	k_o,s^{-1}
0.261	4.71 ± 0.09
0.523	5.57 ± 0.24
0.784	6.16 ± 0.14
1.045	6.96 ± 0.59
1.306	7.55 ± 0.20

slope = 2.70 ± 0.10 l $mol^{-1}s^{-1}$
intercept = 4.07 ± 0.09 s^{-1}

Table2.14 dependence of k_o on [i-propanol]

($[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.052M)

[i-PrOH],M	k_o, s^{-1}
0.130	2.37 ± 0.10
0.261	2.44 ± 0.02
0.523	2.53 ± 0.01
0.784	2.72 ± 0.04
1.045	2.88 ± 0.19

slope = 0.551 ± 0.038 l $mol^{-1}s^{-1}$
intercept = 2.284 ± 0.024 s^{-1}

Table 2.15 dependence of k_o on acidity

($[NaNO_2]$ = 0.01M, [i-PrOH] = 0.261M)

$[H^+]_{xs}$ x10^2,M	k_o,s^{-1}
3.82	1.92
8.64	4.22
13.46	6.33
18.28	10.49
23.10	12.75

Table 2.16 dependence of k_o on [t-butanol]

($[NaNO_2]$ = 0.04M, $[H^+]_{xs}$ = 0.0554M)

[t-BuOH],M	k_o, s^{-1}
0.784	5.83 ± 0.16
1.045	5.66 ± 0.24

Table 2,17 dependence of k_o upon [ethanediol]

($[NaNO_2]$ = 0.04M, $[H^+]_{xs}$ = 0.066M)

[ethanediol],M	k_o, s^{-1}
0.090	24.6 ± 1.5
0.179	27.3 ± 2.0
0.269	30.4 ± 7.7
0.358	32.6 ± 0.4
0.448	33.4 ± 1.0

slope = 30.32 ± 1.27 l $mol^{-1}s^{-1}$

intercept = 21.93 ± 0.31 s^{-1}

Table 2.18 dependence of k_o on acidity

($[NaNO_2]$ = 0.04M, [ethanediol] = 0.269M)

$[H^+]_{xs} \times 10^2$,M	k_o, s^{-1}
4.9	21.2 ± 0.9
6.6	31.8 ± 1.1
8.4	47.3 ± 2.7
9.8	58.3 ± 2.5
13.2	81.7 ± 2.3

slope = 742 ± 20 l $mol^{-1}s^{-1}$

Table 2.19 dependence of k_o on [glycerol] at 25°C

([$NaNO_2$] = 0.04M, [H^+] = 0.066M)

[glycerol],M	k_o, s^{-1}
0.210	36.6 ± 2.9
0.264	39.4 ± 3.1
0.317	38.3 ± 3.1
0.419	43.4 ± 2.0
0.524	41.5 ± 0.6

slope = 17.1 ± 7.3 l $mol^{-1}s^{-1}$
intercept = 33.9 ± 2.7 s^{-1}

Table 2.20 dependence of k_o on [glycerol] at 0°C

([$NaNO_2$] = 0.04M, $[H^+]_{xs}$ = 0.066M)

[glycerol],M	k_o, s^{-1}
0.108	3.66 ± 0.11
0.216	3.33 ± 0.27
0.324	4.32 ± 0.15
0.432	4.56 ± 0.21

slope = 2.82 ± 0.21 l $mol^{-1}s^{-1}$
intercept = 3.37 ± 0.07 s^{-1}

Table 2.21 dependence of k_o on acidity at 0°C

([glycerol] = 0.216M, [$NaNO_2$] = 0.04M)

$[H_2SO_4]x10^2$,M	$[H^+]_{xs}$ $x10^2$,M	k_o,s^{-1}
3.75	4.9	2.1 ± 0.2
5.00	6.6	3.3 ± 0.3
7.50	9.8	6.8 ± 0.7
10.00	13.2	9.0 ± 0.8
12.5	16.5	12.8 ± 0.9

slope = 91.0 ± 4.5 l $mol^{-1}s^{-1}$

Table 2.22 dependence of k_o on [mannitol]

($[NaNO_2]$ = 0.04M, $[H^+]_{xs}$ = 0.066M)

[mannitol],M	k_o, s^{-1}
0.198	32.1 ± 2.8
0.297	36.6 ± 2.7
0.347	39.1 ± 3.6
0.396	31.8 ± 5.0

slope = 46.8 ± 1.1 l $mol^{-1}s^{-1}$
intercept = 22.8 ± 0.3 s^{-1}

Table 2.23 dependence of k_o on acidity

($[NaNO_2]$ = 0.04M, [mannitol] = 0.160M)

$[H_2SO_4] \times 10^2$,M	$[H^+]_{xs} \times 10^2$,M	k_o, s^{-1}
3.75	4.9	20.5 ± 1.4
5.00	6.6	37.1 ± 3.2
7.50	9.8	52.4 ± 8.8
10.0	13.2	65.9 ± 13.8

slope = 525 ± 70 l $mol^{-1}s^{-1}$

Table 2.24 dependence of k_o upon [glucose]

($[NaNO_2] = 4.0 \times 10^{-3}$M, $[H^+]_{xs}$ = 0.0908M)

[glucose],M	k_o, s^{-1}
0.100	8.47 ± 0.31
0.150	9.10 ± 0.34
0.200	9.81 ± 0.46
0.251	10.0 ± 0.4

slope = 10.70 ± 1.6 l $mol^{-1}s^{-1}$
intercept = 7.48 ± 0.28 s^{-1}

Table 2.25 dependence of k_o on acidity

($[NaNO_2]$ = 0.04M, [sucrose] = 0.20M, (H_2SO_4))

$[H^+]_{xs}$ x10^2,M	k_o, s^{-1}
0.9	2.27 ± 0.20
2.6	4.53 ± 0.41
5.8	7.84 ± 1.02
9.2	11.97 ± 1.80
12.5	19.9 ± 2.0

slope = 144 ± 15 l $mol^{-1}s^{-1}$

Table 2.26 variation of k_o with [sucrose]

($[NaNO_2]$ = 4.0 x10^{-3}M, $[H^+]_{xs}$ = 0.0908M)

[sucrose],M	k_o, s^{-1}
0.059	6.47 ± 0.19
0.118	7.28 ± 0.21
0.177	7.54 ± 0.25
0.236	8.03 ± 0.34
0.295	8.29 ± 0.24

slope = 9.69 ± 1.25 l $mol^{-1}s^{-1}$
intercept = 5.96 ± 0.20 s^{-1}

Table 2.27 variation of k_o with [methanol] and [chloride ion]

($[H^+]_{xs}$ = 0.052(H_2SO_4), [$NaNO_2$] = 0.04M)

[methanol],M	[KCl],M	k_o, s^{-1}
0.198	0	37.5 ± 2.5
	0.2	45.2 ± 4.7
	0.4	57.7 ± 4.4
	0.6	66.8 ± 8.3
	0.8	73.4 ± 8.1
	1.0	98.4 ± 10.7
0.395	0	49.3 ± 5.2
	0.2	61.9 ± 3.6
	0.4	75.0 ± 4.0
	0.6	80.4 ± 6.0
	0.8	105.7 ± 2.4
	1.0	105.0 ± 1.4
0.593	0	51.4 ± 5.0
	0.2	65.2 ± 6.0
	0.4	70.4 ± 5.3
	0.6	84.0 ± 5.3
	0.8	95.4 ± 6.7
	1.0	109.3 ± 5.1
0.790	0	57.4 ± 3.7
	0.2	65.6 ± 5.4
	0.4	72.1 ± 9.5
	0.6	88.8 ± 5.3
	0.8	105.1 ± 1.7
	1.0	109.9 ± 7.7

Table 2.28 slopes and intercepts of plots of k_o against the chloride ion concentration.

[MeOH],M	slope,l $mol^{-1}s^{-1}$	intercept,s^{-1}
0.198	51.6 ± 2.0	56.5 ± 1.0
0.395	54.2 ± 3.1	50.4 ± 1.7
0.593	56.1 ± 2.8	51.2 ± 1.7
0.790	53.8 ± 4.0	55.1 ± 2.2

Table 2.29 dependence of k_o upon [methanol] in the absence of bromide ions.

($[NaNO_2]$ = 0.01M, $[H^+]$ = 0.052M)

[MeOH],M	k_o, s^{-1}
0.124	1.77 ± 0.13
0.247	2.39 ± 0.20
0.494	3.81 ± 0.17
0.741	4.23 ± 0.08

slope = 3.90 ± 0.21 l $mol^{-1}s^{-1}$
intercept = 1.35 ± 0.10 s^{-1}

Table 2.30 variation of k_o with [methanol] at 0°C

($[KCl]$ = 0.50M, $[H^+]_{xs}$ = 0.052M)

[MeOH],M	k_o, s^{-1}
0.124	3.80 ± 0.41
0.247	4.19 ± 0.25
0.494	5.48 ± 0.46
0.741	6.34 ± 0.60
0,989	6.97 ± 0.18

slope = 4.28 ± 0.28 l $mol^{-1}s^{-1}$
intercept = 3.24 ± 0.13 s^{-1}

Table 2.31 variation of k_o in the absence of halide ions at 0°C for the nitrosation of methol

($[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.0848M)

[MeOH],M	k_o, s^{-1}
0.247	4.17 ± 0.23
0.494	5.74 ± 0.10
0.741	6.93 ± 0.15
0.988	8.20 ± 0.16

slope = 5.38 ± 0.23 l $mol^{-1}s^{-1}$
intercept = 2.94 ± 0.16 s^{-1}

Table 2.32 variation of k_o with [MeOH] in the presence of chloride ions.

([NaCl] = 0.440M, $[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.0686M)

[MeOH],M	k_o, s^{-1}
0.247	5.59 ± 0.11
0.494	7.16 ± 0.07
0.741	8.90 ± 0.14
0.988	9.87 ± 0.21

slope = 5.90 ± 0.46 l $mol^{-1}s^{-1}$

intercept = 4.24 ± 0.31 s^{-1}

Table 2.33 dependence of k_o on $[Br^-]$ and $[H^+]$
($[MeOH] = 0.124M$, $[NaNO_2] = 0.04M$)

$[H^+] \times 10^2$, M	$[Br^-]$, M	k_o, s^{-1}
0.9	0	9.8 ± 0.5
	0.2	15.0 ± 0.6
	0.4	17.4 ± 0.7
	0.6	22.0 ± 1.6
	0.8	25 6 ± 1.6
3.2	0	21.3 ± 1.2
	0.2	26.2 ± 1.9
	0.4	35.0 ± 4.0
	0.6	42.6 ± 0.7
	0.8	47.2 ± 6.1
9.8	0	66.0 ± 5.3
	0.2	75.0 ± 13.6
	0.4	107 ± 11
	0.6	152 ± 7
	0.8	180 ± 13

Table 2.35 dependence of k_o on $[Br^-]$ and $[H^+]$

[MeOH] = 0.372M

$[H^+]$ x10^2,M	$[Br^-]$,M	k_o, s^{-1}
0.9	0	15.6 ± 0.5
	0.2	22.7 ± 0.3
	0.4	27.7 ± 0.3
	0.6	33.0 ± 2.7
	0.8	37.9 ± 0.9
3.2	0	25.3 ± 1.5
	0.4	46.3 ± 2.6
	0.6	53.2 ± 7.0
	0.8	61.8 ± 2.1
5.4	0	40.3 ± 2.3
	0.2	51.9 ± 4.0
	0.4	66.6 ± 2.7
	0.6	74.2 ± 7.1
	0.8	85.9 ± 8.2
9.8	0	69.1 ± 11.1
	0.2	88.5 ± 8.0
	0.4	122.8 ± 1.6
	0.6	164 ± 11
	0.8	188 ± 3

Tabla 2.36 dependence of k_o on $[Br^-]$ and $[H^+]$

[MeOH] = 0.494M

$[H^+]$ x10^2,M	$[Br^-]$,M	k_o, s^{-1}
0.9	0	12.6 ± 0.8
	0.2	20.0 ± 1.2
	0.4	24.0 ± 0.3
	0.6	29.9 ± 2.1
	0.8	34.3 ± 1.2
3.2	0	29.7 ± 0.9
	0.2	39.7 ± 2.2
	0.4	49.1 ± 2.6
	0.6	57.9 ± 10.4
	0.8	63.9 ± 6.9
5.4	0	47.2 ± 2.8
	0.2	60.4 ± 3.6
	0.4	76.6 ± 4.3
	0.6	77.9 ± 8.9
	0.8	108 ± 11
9.8	0	77.7 ± 11.1
	0.2	105.1 ± 7.8
	0.4	135.4 ± 13.9
	0.6	163 ± 4
	0.8	208 ± 7

Table 2.37 graphs of k_o against [bromide ion]

[MeOH],M	$[H^+]x10^2$,M	slope $l\ mol^{-1}s^{-1}$	intercept,s^{-1}
0.124	0.9	19.3 ± 1.1	10.2 ± 0.5
"	3.2	34.1 ± 2.1	20.8 ± 1.0
"	5.4	55.6 ± 5.2	30.0 ± 0.5
"	9.8	121 ± 19	42.5 ± 9.4
0.247	3.2	34.8 ± 3.8	20.9 ± 1.9
"	5.4	81.4 ± 10.9	32.4 ± 5.4
"	9.8	152 ± 17	55 ± 8.4
0.372	0.9	27.4 ± 1.2	16.4 ± 0.6
"	3.2	45.4 ± 2.7	26.2 ± 1.5
"	5.4	56.8 ± 2.9	41.0 ± 1.4
"	9.8	156 ± 10	63.8 ± 5.0
0.494	0.9	26.2 ± 1.5	13.5 ± 0.7
"	3.2	43.3 ± 2.2	30.7 ± 1.1
"	5.4	69.6 ± 11.0	46.2 ± 5.4
"	9.8	159 ± 10	74.0 ± 4.6

Table 2.38 graphs of slope(k_o against [Br^-]) against [H^+]

[MeOH],M	slope $l^2mol^{-2}s^{-1}$
0.124	1161 ± 143
0.247	1751 ± 127
0.372	1454 ± 315
0.494	1522 ± 185

slope = 1003 ± 91 $l^3mol^{-3}s^{-1}$

intercept = 1047 ± 33 $l^2mol^{-2}s^{-1}$

Table 2.39 graphs of intercept(k_o against $[Br^-]$) against $[H^+]$

[MeOH],M	slope, $l\ mol^{-1}s^{-1}$
0.124	359 ± 32
0.247	411 ± 88
0.372	543 ± 24
0.494	677 ± 20

slope = 879 ± 114 $l^2mol^{-2}s^{-1}$
intercept = 225 ± 38 $l\ mol^{-1}s^{-1}$

Table 2.40 dependence of k_o on [Methanol] at 0°C

($[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.052M, [KBr] = 0.50M)

[MeOH],M	k_o, s^{-1}
0.124	3.59 ± 0.31
0.247	5.13 ± 0.28
0.494	6.92 ± 0.54
0.741	7.67 ± 0.30

slope = 6.5 ± 1.2 $l\ mol^{-1}s^{-1}$
intercept = 3.23 ± 0.56 s^{-1}

($[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.0686M, [NaBr] = 0.50M)

[MeOH],M	k_o, s^{-1}
0.247	6.95 ± 0.27
0.494	9.10 ± 0.07
0.741	10.62 ± 0.13
0.988	11.3 ± 0.9

slope = 7.44 ± 0.73 $l\ mol^{-1}s^{-1}$
intercept = 5.21 ± 0.39 s^{-1}

Table 2.41 dependence of k_o on [i-propanol]
no halide ions present

($[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.052M)

[i-PrOH],M	k_o, s^{-1}
0.130	2.37 ± 0.10
0.261	2.44 ± 0.02
0.522	2.53 ± 0.01
0.784	2.72 ± 0.04
1.045	2.88 ± 0.19

slope = 0.548 ± 0.008 l $mol^{-1}s^{-1}$
intercept = 2.291 ± 0.005 s^{-1}

Table 2.42 dependence of k_o on [i-propanol]

($[KCl]$ = 0.50M, $[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.052M)

[i-PrOH],M	k_o s^{-1}
0.130	3.70 ± 0.17
0.261	4.00 ± 0.40
0.522	4.36 ± 0.14
0.784	4.64 ± 0.17
1.045	5.03 ± 0.28

slope = 1.30 ± 0.06 l $mol^{-1}s^{-1}$
intercept = 3.67 ± 0.04 s^{-1}

Table 2.43 dependence of k_o on [i-propanol] for solutions containing 0.5M potassium bromide.

($[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.052M)

[i-PrOH],M	k_o, s^{-1}
0.130	3.92 ± 0.26
0.261	4.45 ± 0.54
0.522	5.13 ± 0.26
0.784	5.87 ± 0.43
1.045	6.01 ± 0.67

slope = 2.90 ± 0.15 l $mol^{-1}s^{-1}$
intercept = 3.61 ± 0.08 s^{-1}

Table 2.44 dependence of k_o on [i-propanol] in the absence of halide ions.

($[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.0848M)

[i-PrOH],M	k_o,s^{-1}
0.261	4.27 ± 0.07
0.522	4.79 ± 0.08
0.784	5.10 ± 0.05
1.045	5.40 ± 0.20
1.306	5.71 ± 0.20

slope = 1.34 ± 0.09 l $mol^{-1}s^{-1}$
intercept = 4.00 ± 0.08 s^{-1}

k_3 = 15.8 ± 1.1 $l^2mol^{-2}s^{-1}$
k_{-2} = 47.2 ± 1.0 l $mol^{-1}s^{-1}$

Table 2.45 nitrosation of i-propanol in the presence of chloride ions.

([NaCl] = 0.440M, $[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.0686M)

[i-PrOH],M	k_o, s^{-1}
0.261	5.48 ± 0.29
0.522	5.74 ± 0.06
0.784	6.14 ± 0.13
1.045	7.12 ± 0.41
1.306	7.36 ± 0.40

slope = 2.64 ± 0.65 l $mol^{-1}s^{-1}$
intercept = 5.89 ± 0.47 s^{-1}

Table 2.46 nitrosation of i-propanol in the presence of bromide ions.

([NaBr] = 0.50M, $[NaNO_2]$ = 0.01M, $[H^+]_{xs}$ = 0.0686M)

[i-PrOH],M	k_o, s^{-1}
0.261	6.78 ± 0.08
0.522	6.85 ± 0.30
0.784	8.23 ± 0.27
1.045	8.62 ± 0.30

slope = 2.64 ± 0.65 l $mol^{-1}s^{-1}$
intercept = 5.89 ± 0.47 s^{-1}

CHAPTER THREE.

THE EFFECT OF ADDITIVES ON THE NITROSATION OF N-METHYLANILINE AND p-NITRO N-METHYLANILINE.

3.1 Introduction.

There is currently much interest in the kinetics of the formation of N-nitrosamines, largely on account of their potential activity as carcinogens and the possibility of their formation in the environment and in vivo from the reaction between secondary amines and nitrous acid.

For reactions in aqueous acidic solution, the catalysis of the nitrosation reaction by halide ions and thiocyanate ion has been established [16]; more recently, the catalytic activity of thiourea has also been demonstrated[35]. The mechanistic details of these reactions have been established and the catalysis is now known to be the result of the formation of the nitrosyl halide, nitrosyl thiocyanate or S-nitroso thiourea cation which nitrosate amines with greater efficiency than nitrous acid. The extent of the catalysis is largely dependent upon the equilibrium constant for the formation of the new nitrosating agent. The inhibition of nitrosamine formation has also received much attention. The activity of the inhibitors lies in their ability to undergo irreversible and rapid reactions with the nitrosating agent, reactions which occur in direct competition with the nitrosation of the amine. Many of these so-called nitrite traps have now been identified, the most efficient ones being (in order of efficiency):

HN_3 > hydrazine > NH_2SO_3H > ascorbic acid > hydroxylamine > urea

The relative reactivities of these species have been established by means of an indirect method developed by

Williams[49] and based upon the denitrosation of N-methyl N-nitrosoaniline.

In relation to the identification of nitrite traps, it was decided to investigate the effect, if any, of the addition of alcohols, carbohydrates, phenols, ethers and thiols upon the nitrosation of N-methylaniline (NMA) or p-nitro N-methylaniline (pNNMA). In the case of the alcohols it is well known that the alkyl nitrite is rapidly formed upon the addition of alcohols to aqueous acidified sodium nitrite solutions[111]. Equilibrium measurements have now been made by direct methods for several alcohols (chapter 2 of this thesis). Stedman and co-workers have demonstrated that the thiol cysteine undergoes rapid S-nitrosation[95] and it appears that the equilibrium constants for the formation of the thionitrites are several orders of magnitude greater than for the alkyl nitrites. The thionitrite reaction is, in fact, regarded as irreversible.

3.2 The effect of added alcohols and carbohydrates on the nitrosation of N-methylaniline.

3.2.1 The nitrosation of N-methylaniline in the absence of additives .

The nitrosation of N-methylaniline (NMA) has been studied in detail by Ridd and other workers; the subject is discussed in depth in the review by Ridd[16]. A summary of the important features of the kinetics of nitrosation of NMA is given below:

The nitrosation of NMA with nitrous acid in aqueous perchloric acid was investigated by Kalatzis and Ridd[8]. The

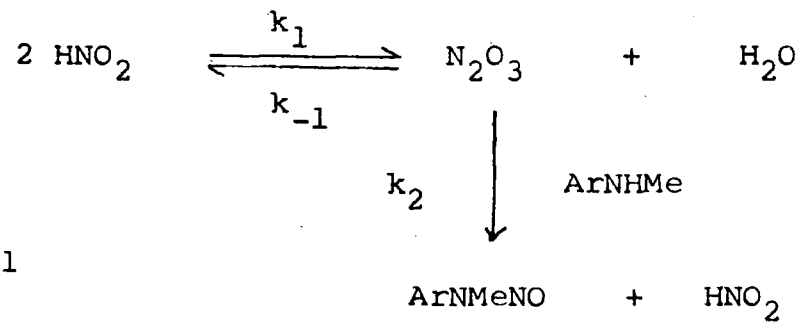
reaction was studied over a wide range of acidity and the results indicated that the reaction mechanism was highly sensitivetowards the acidity of the reaction solutions:

At low acidity (i.e. $[H^+]$ < ca. 0.1M) it was shown that the rate of reaction was independent of the amine concentration and that the initial rate of reaction varied with the square of the initial nitrous acid concentration. The results were consistent with a reaction mechanism involving the nitrosation of NMA by nitrous anhydride (which was formed rather slowly)asshown in Scheme 1 and where $k_{-1} << k_2[ArNHMe]$.

With increasing acidity the rate of reaction increased, the total order of reaction increased from two to three and the rate expression given in equation 3.1 was established.

$$\text{rate} = k[\text{amine}][\text{nitrous acid}]^2 \qquad 3.1$$

These results were also found to be consistent with the mechanism in Scheme 1 provided that now $k_{-1} >> k_2[ArNHMe]$.



Scheme 1

At even higher acidity (>0.1M) the total order of reaction decreased and the rate expression in equation 3.2 was established.

$$\text{rate} = k'[\text{amine}][\text{nitrous acid}] \qquad 3.2$$

The transition from overall third order to second order

kinetics was found to be completed in 3M perchloric acid. This meant that the nitrous anhydride had been replaced by the nitrous acidium ion as the effective nitrosating agent and the replacement was complete in 3M perchloric acid.

Kalatzis and Ridd also established that at low acidities the nitrosation of NMA occurred via the unprotonated form of the amine. They found zero order (w.r.t. amine) kinetics up to 0.1M perchloric acid but in the present work , with the nitrite in large excess, plots of $\ln(A-A_\infty)$ against time were linear, indicating a first order dependence upon the amine. Had the situation been the same as that found by Kalatzis and Ridd then if the formation of the nitrous anhydride were rate determining then the reaction would be zero order with respect to the amine and this would have been indicated by a linear dependence of the optical density with respect to time.

3.2.2. The nitrosation of N-methylaniline in the presence of alcohols and carbohydrates.

For reaction in the absence of additives it was established that for the selected experimental conditions the nitrosation of NMA was taking place via the nitrous anhydride mechanism as proposed by Kalatzis and outlined in Scheme 1, where $k_{-1} << k_2[ArNHMe]$. Kinetic measurements were made under first order conditions with a large excess (> 10 fold) of nitrous acid. Reactions were carried out at 31°C in the cell of a visible-uv spectrophotometer.

The dependence of k_o upon the initial total nitrite

concentration was investigated for the reaction in the absence of additives. The results are presented in the table below:

Variation of k_o with the nitrite concentration.

$[NMA] = 1.86 \times 10^{-4}M$
$[H_2SO_4] = 0.078M$

$[H^+]$ $\times 10^2$,M	$[NaNO_2]$ $\times 10^3$M	$k_o \times 10^3$,M	$k_o' \times 10^3$,M
9.93	0.45	0.54	0.54
9.88	1.00	1.58	1.59
9.83	1.49	4.26	4.30
9.73	2.47	16.2	16.5
9.63	3.50	22.1	22.8
9.60	3.79	35.6	36.8
9.47	5.02	40.5	42.4
9.41	5.69	48.1	51.1

k_o values were adjusted to allow for the change in acidity due to the removal of hydrogen ions by protonation of the nitrite ion. A graph of log k_o' against log[total nitrite] is shown in figure 1.

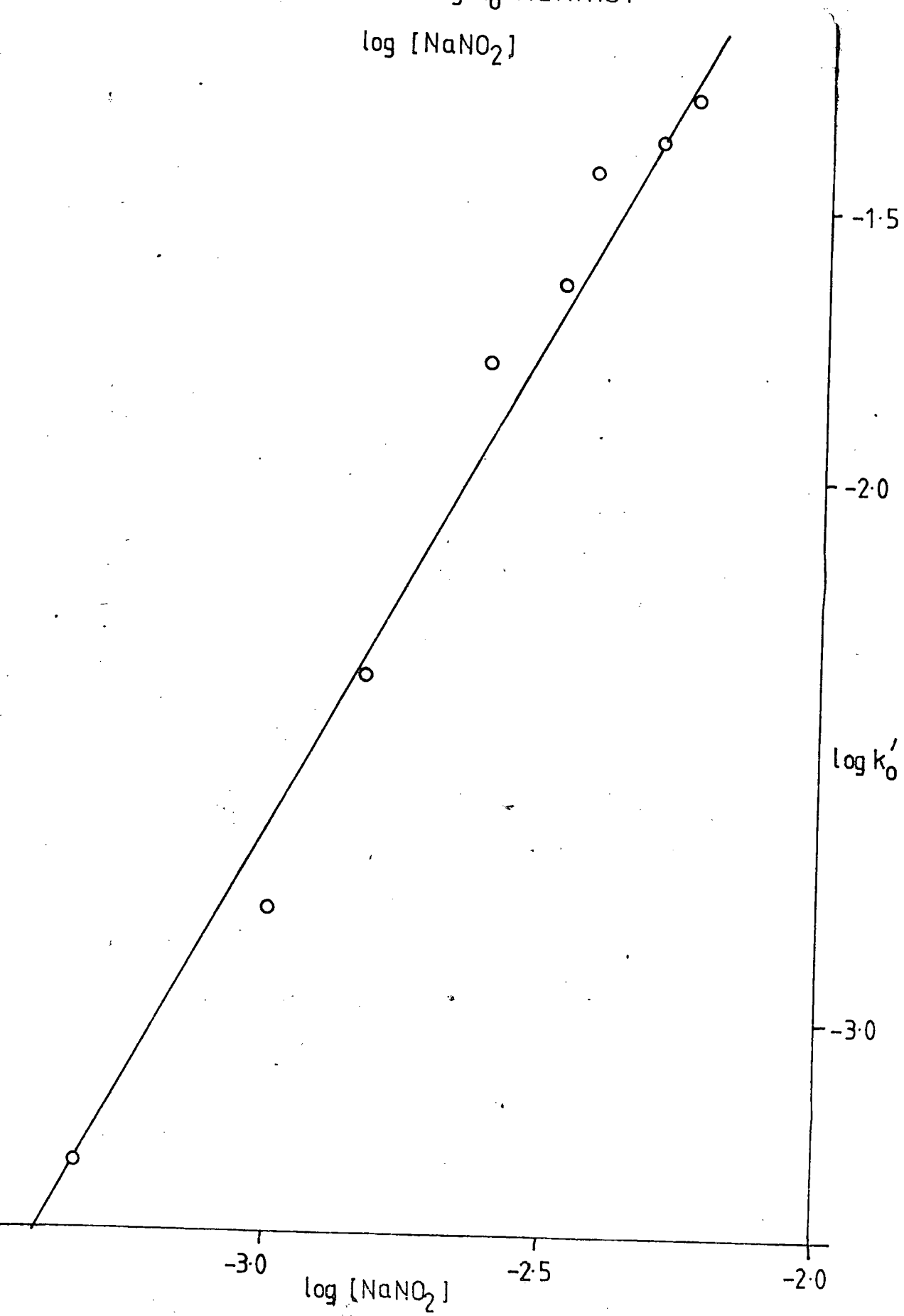
If n is the total order with respect to the total nitrite then

$$k_o = k_1[\text{total nitrite}]^n$$

A plot of log k_o against log[total nitrite] should then be linear and the slope of the plot should give the order with respect to the total nitrite concentration.

The graph of log k' was linear and the slope of the graph was 1.91, indicating second order with respect to the

FIGURE 1 - GRAPH OF log k_o' AGAINST log [$NaNO_2$]



nitrite.

For the reactions in the presence of the alcohols the concentrations of reagents were as follows:

$$[NaNO_2] = 6.00 \times 10^{-3} M$$

$$[NMA] = 1.86 \times 10^{-4} M$$

$$[H_2SO_4] = 0.078 M$$

and for reactions in the presence of the carbohydrates the concentrations of reagents were:

$$[NaNO_2] = 1.97 \times 10^{-3} M$$

$$[HClO_4] = 3.68 \times 10^{-2} M$$

$$[NMA] = 1.86 \times 10^{-4} M$$

the addition of alcohols and carbohydrates had the effect of decreasing the observed first order rate coefficient, k_o. The results for the variation of k_o with six alcohols and five carbohydrates are shown in tables 3.1 to 3.12.

Table 3,1 Nitrosation of NMA in the presence of methanol.

[MeOH],M	$k_o \times 10^3, s^{-1}$	$(k_o)^{-\frac{1}{2}}$
0	43.60	4.78
0.247	20.25	7.03
0.494	11.67	9.26
0.642	9.72	11.24
0.742	6.94	12.00
0.989	4.78	14.46

Table 3.2 Nitrosation of NMA in the presence of ethanol.

[EtOH],M	k_o x10^2,s^{-1}	$(k_o)^{-\frac{1}{2}}$
0	4.81	4.56
0.249	3.68	5.22
0.498	2.78	6.00
0.747	1.92	7.21
0.996	1.59	7.92

Table 3.3 Nitrosation of NMA in the presence of n-propanol.

[nPrOH],M	k_o x10^2,s^{-1}	$(k_o)^{-\frac{1}{2}}$
0	5.79	4.15
0.250	3.29	5.51
0.500	2.53	6.28
0.750	1.52	8.11
1.000	1.46	8.27

Table 3.4 Nitrosation of NMA in the presence of i-propanol.

[iPrOH],M	k_o x10^2,s^{-1}	$(k_o)^{-\frac{1}{2}}$
0	5.09	4.43
0.250	4.33	4.81
0.500	3.72	5.18
0.750	3.52	5.33
1.000	3.28	5.52

Table 3.5 Nitrosation of NMA in the presence of ethanediol.

[ethanediol],M	k_o x10^2,s^{-1}	$(k_o)^{-½}$
0	4.78	4.57
0.279	4.41	4.76
0.558	2.15	6.82
0.837	1.85	7.35
0.986	1.55	8.03

Table 3.6 Nitrosation of NMA in the presence of 1,3propanediol.

[propanediol],M	k_o x10^2, s^{-1}	$(k_o)^{-½}$
0	4.69	4.62
0.247	2.60	6.20
0.493	1.67	7.74
0.740	1.00	10.01
0.986	0.68	12.10

Table 3.7 Nitrosation of NMA in the presence of methanol under the conditions used for the reactions in the presence of sugars.

[MeOH],M	k_o x10^2, s^{-1}	$(k_o)^{-½}$
0	8.54	10.82
0.121	4.65	14.66
0.242	3.38	17.20
0.363	2.51	19.96
0.484	1.89	23.00

Table 3.8 Nitrosation of NMA in the presence of mannitol.

[mannitol],M	k_o x10^3,s^{-1}	$(k_o)^{-½}$
0	9.23	10.4
0.097	7.29	11.7
0.203	5.80	13.1
0.293	4.53	14.8
0.380	3.87	16.1

Table 3.9 Nitrosation of NMA in the presence of D(+)glucose.

[glucose],M	k_o x10^3,s^{-1}	$(k_o)^{-½}$
0	8.24	11.0
0.095	6.51	12.4
0.203	6.31	12.6
0.300	5.03	14.1
0.381	6.04	12.9

Table 3.10 Nitrosation of NMA in the presence of lactose.

[lactose],M	k_o x10^3,s^{-1}	$(k_o)^{-½}$
0	8.02	11.2
0.115	8.06	11.1
0.158	7.76	11.4
0.212	7.03	11.9
0.310	6.22	12.7

Table 3.11 Nitrosation of NMA in the presence of sucrose.

[sucrose],M	$k_o \times 10^3, s^{-1}$	$(k_o)^{-\frac{1}{2}}$
0	8.37	10.9
0.106	7.88	11.3
0.155	6.77	12.2
0.207	6.64	12.3
0.310	5.78	13.2

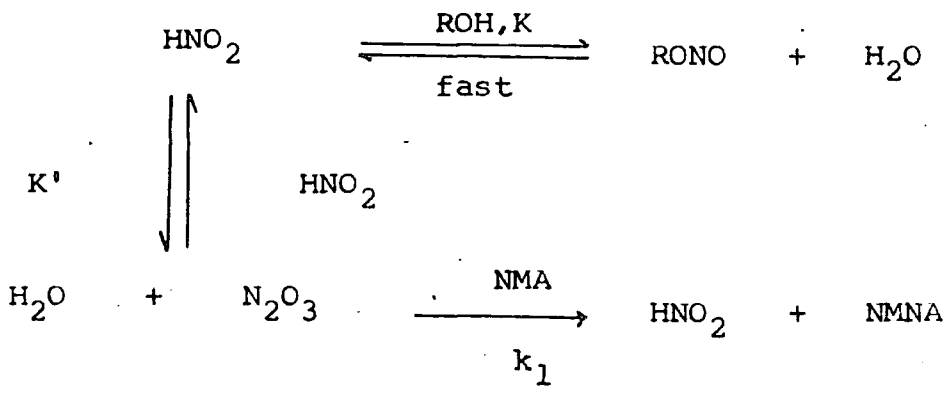
Table 3,12 Nitrosation of NMA in the presence of maltose.

[maltose],M	$k_o \times 10^3, s^{-1}$	$(k_o)^{-\frac{1}{2}}$
0	9.65	10.2
0.115	7.84	11.3
0.147	7.33	11.7
0.207	6.83	12.1
0.265	6.13	12.8

Looking at the results for methanol in table 3.1 a marked reduction in k_o with increasing methanol concentration is observed. The other alcohols and the carbohydrates also show decreases in k_o with increasing alcohol (or carbohydrate) concentration but the decreases are less marked.

The experimental results may be satisfactorily accounted for on the basis of a mechanism in which the equilibrium between the nitrous acid, the alcohol or carbohydrate and the alkyl nitrite is established and in which the alkyl nitrite is ineffective as a nitrosating agent. In another section of this thesis (chapter 4) it has

been demonstrated that in acidic conditions in the absence of nucleophiles n-propyl nitrite is quite ineffective as a nitrosating agent; the behaviour of alkyl nitrites as nitrosating agents appears to rely upon their first reacting to produce an effective nitrosating agent such as nitrous acid or a nitrosyl halide. The mechanism proposed for the nitrosation of NMA in the presence of alcohols (or carbohydrates) is outlined in Scheme 2:



Scheme 2

For the selected experimental conditions the rate expression in equation 3.3 was established. Since it is indicated that the alkyl nitrite is almost totally

$$\text{rate} = k_o[\text{NMA}] \qquad 3.3$$

ineffective as a nitrosating agent and if reaction occurs via nitrous anhydride the total rate of reaction may also be expressed by equation 3.4

$$\text{rate} = k_1K'[\text{NMA}][\text{HNO}_2]^2 \qquad 3.4$$

Assuming that the concencentration of the nitrous anhydride is negligibly small (this is reasonable since the equilibrium constant for the self dehydration of nitrous acid is small) and that the equilibrium:

$$ROH + HNO_2 \rightleftharpoons RONO$$

is established very rapidly and is maintained then the nitrous acid concentration may be expressed in terms of the total nitrite concentration and the equilibrium constant, K, for the formation of the alkyl nitrite from nitrous acid and the alcohol (equation 3.5)

$$[HNO_2] = \frac{[TN]}{1 + K[ROH]} \qquad 3.5$$

The total rate of reaction may therefore be expressed by equation 3.6 and so k_o may be expressed by equation 3.7

$$\text{total rate} = k_1K'[NMA]\left(\frac{[TN]}{1 + K[ROH]}\right)^2 \qquad 3.6$$

$$k_o = k_1K'\left(\frac{[TN]}{1 + K[ROH]}\right)^2 \qquad 3.7$$

Taking the reciprocal of equation 3.7 leads to equation 3.8 and from equation 3.8 it is indicated that a plot of $k_o^{-\frac{1}{2}}$ against the alcohol (or carbohydrate) concentration should be linear

$$k_o^{-\frac{1}{2}} = \frac{1}{[TN](k_1K')^{\frac{1}{2}}} + \frac{K[ROH]}{[TN](k_1K')^{\frac{1}{2}}} \qquad 3.8$$

Moreover, the ratio of the slope to the intercept of this graph should give the equilibrium constant, K, for the formation of the alkyl nitrite. Figure 2 shows two typical sets of results - those for ethanol and methanol. Details of the graphs are given in table 3.13. The slopes and intercepts quoted are the best values calculated by means of the principle of least squares. The equilibrium constants for the

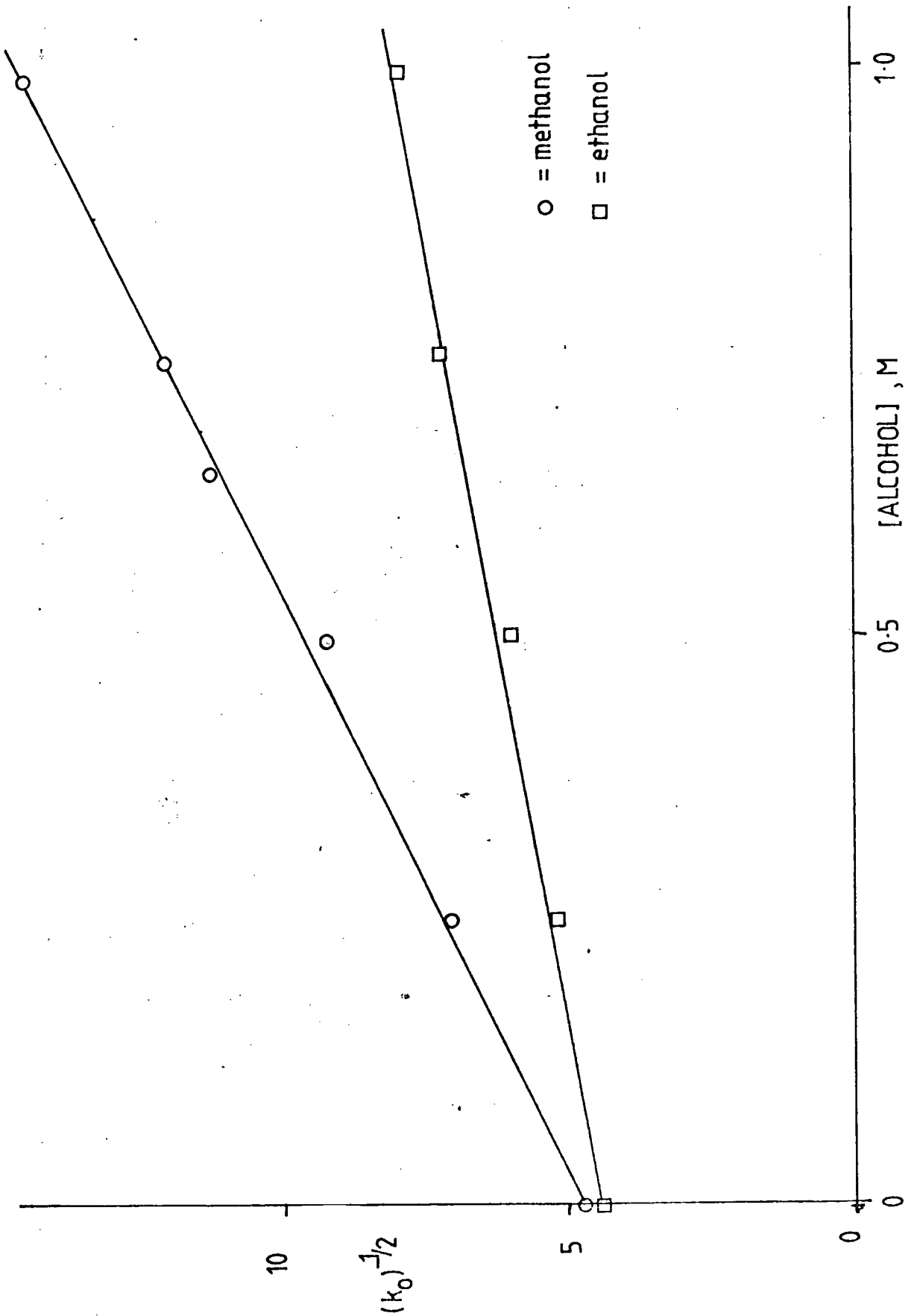


FIGURE 2 - PLOTS OF $(k_o)^{-1/2}$ AGAINST [ALCOHOL]

formation of the alkyl nitrites determined in these experiments are given in table 3.14. The values of the equilibrium constants are for a temperature of 31°C whereas the values quoted in chapter 2 (for the direct measurement of the equilibrium constants) were for temperatures of 25°C or 0°C. However, the equilibrium constants determined indirectly do appear to be in reasonable agreement with the equilibrium constants determined by direct methods.

Table 3.13: details of plots of $k_o^{-\frac{1}{2}}$ against [ROH].

alcohol (or carbohydrate)	slope	intercept
methanol	9.89 ± 0.25	4.66 ± 0.15
ethanol	3.40 ± 0.21	4.44 ± 0.13
n-propanol	4.01 ± 0.25	4.30 ± 0.14
i-propanol	1.08 ± 0.13	4.51 ± 0.08
ethanediol	3.42 ± 0.30	4.65 ± 0.21
1,3 propanediol	7.18 ± 0.49	4.48 ± 0.22
methanol	24.51 ± 0.97	11.20 ± 0.29
mannitol	15.14 ± 0.58	10.27 ± 0.14
glucose	9.36 ± 1.91	11.1 ± 0.4
lactose	8.31 ± 0.22	10.12 ± 0.05
sucrose	7.27 ± 0.63	10.93 ± 0.13
maltose	9.63 ± 0.39	10.20 ± 0.07

Table 3.14 equilibrium constants for alkyl nitrite formation.

alcohol (carbohydrate)	K, l mol^{-1}
methanol	2.12 ± 0.12, 2.19 ± 0.14
ethanol	0.79 ± 0.07
n-propanol	0.93 ± 0.09
i-propanol	0.24 ± 0.03
ethanediol	0.73 ± 0.10
1,3 propanediol	1.60 ± 0.19
mannitol	1.47 ± 0.08
glucose	0.84 ± 0.20
lactose	0.82 ± 0.03
sucrose	0.66 ± 0.06
maltose	0.94 ± 0.05

Schmid and Riedl have developed a similar indirect method for the determination of the equilibrium constants for the formation of alkyl nitrites[83]; their method was based upon the nitrosation of phenols using nitrous acid in the presence of alcohols. Rate measurements were made by removing samples of the reaction solution at various time intervals. The samples were quenched by running them into alkali and then the absorbance at 340nm (due to the p-nitrosophenol) was measured. They too demonstrated that the alkyl nitrites were quite ineffective for the nitrosation of phenol. The equilibrium constants determined by Schmid and Riedl cannot be compared directly with those determined in this thesis since they have been defined

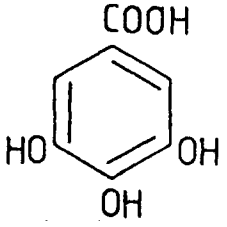
differently. However their results showed the same trends for the series of alcohols - methanol, ethanol, i-propanol.

For the nitrosation of N-methylaniline in the presence of alcohols and carbohydrates in aqueous acidic solutions the results indicate that in all cases the alkyl nitrite was formed and was quite ineffective as a nitrosating agent. In the absence of N-methylaniline spectroscopic evidence for the formation of the alkyl nitrites was obtained: nitrous acid has a characteristic 'hand' - like spectrum[112]. The alkyl nitrites have similar spectra[103] but there are significant differences in the extinction coefficients of the 'fingers' with the result that the formation of the alkyl nitrites resulting from the addition of alcohols (or carbohydrates) to aqueous acidic solutions of nitrous acid could be detected. It was thought, therefore, that in cases where spectroscopic evidence could not be obtained the effect on the rate of nitrosation of N-methylaniline (or a suitable derivative) of the addition of various compounds containing the hydroxyl functional group could be used as evidence for or against the formation of the O-nitroso species.

3.3 The effect of added phenols upon the nitrosation of p-nitro N-methylaniline.

There are reports in the literature that certain phenols have a catalytic effect upon the nitrosation of amines. Walker reported in 1975 that the nitrosation of diethylamine was catalysed by gallic acid (I)[113]. In the same year, Challis and Bartlett reported, incorrectly, the catalysis

of the nitrosation of piperidine by 4-methylcatechol (II) and chlorogenic acid (III).[114] As Walters pointed out[128], these phenols and other similar ones are present in significant concentrations in many foodstuffs but the conditions in the human stomach is very complex, much more so than the models used in the above studies, and so the effect of phenols upon the formation of nitrosamines in the stomach would be much less easily predicted.



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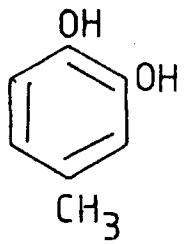

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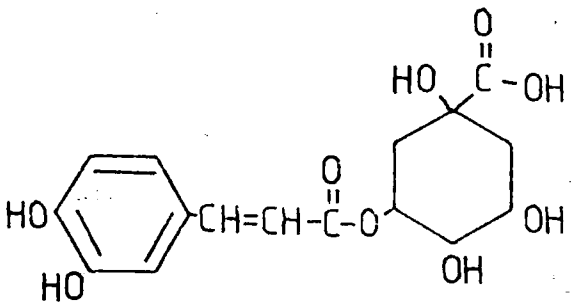


III

However, there are also reports of the inhibition of N-nitrosamine formation by some phenol derivatives[115,116]. In a more recent study, Davies and co-workers reported that p-nitrosophenol catalysed the nitrosation of morpholine and piperidine and that the nitrosation reaction showed a first order dependence upon the p-nitrosophenol[117]. They proposed a mechanism in which the quinone monoxime tautomer of the phenol reacted with the nitrous acid to produce the effective nitrosating agent which then underwent attack by the amine to yield the nitrosamine and the nitrosophenol.

In the present study it was decided to carry out an

investigation into the influence of phenols upon the N-nitrosation of a secondary amine. p-Nitro N-methylaniline was selected as a suitable amine; rate measurements could be taken by following the disappearance of the free amine (an intensely yellow-coloured species) without interference by the nitrosophenol or nitrous acid. Working under first order conditions with the nitrite in excess, rate measurements were made in the absence of phenol and for several phenol concentrations for each phenol studied. The concentrations of the reagents were as follows:

$[HClO_4]$ = 3.667 x10^{-2}M, [pNNMA] = 3.46 x10^{-5}M,

$[NaNO_2]$ = 4.023 x10^{-4}M.

Kinetic runs were carried out at 31°C by monitoring the change in absorbance at 405 or 420nm. The results of experiments are presented in tables 3.15, 3.16, 3.17, and 3.18.

Table 3.15 nitrosation of pNNMA in the presence of phenol.

[phenol],x10^3,M	k_o x10^2, s^{-1}
0	3.04
1.988	2.92
3.976	2.95
5.964	3.19
7.952	3.07

Table 3.16 Nitrosation of pNNMA in the presence of 2,4 xylenol

[2,4 xylenol],M	k_o, s^{-1}
0	3.00
2.213	4.56
4.427	3.61
6.640	4.78
8.854	4.82
13.28	5.32

Table 3.17 Nitrosation of pNNMA in the presence of p-cresol.

[p-cresol],M	k_o, s^{-1}
0	3.00
2,143	3.03
4.826	2.92
7.240	3.29
9.653	3.48
14.48	3.41

Table 3.18 Nitrosation of pNNMA in the presence of p-chlorophenol.

[p-chlorophenol], M.	k_o, s^{-1}
0	3.04
3.663	2.97
7.327	3.10
10.99	3.11
14.65	2.92

From the tables of results it can be seen that, with the exception of 2,4 xylenol, the addition of the phenols had no effect upon the rate of nitrosation of p-nitro N-methylaniline. In the case of the reaction in the presence of 2,4 xylenol a small increase in the first order observed rate coefficient, k_o, was observed. However it is doubtful whether this is a real effect.

In conclusion, it appears that the phenols studied in the present investigation do not catalyse the nitrosation of p-nitro N-methylaniline. It is anticipated that catalysis would also be absent for the nitrosation of other secondary amines.

3.4 The nitrosation of N-methylaniline in the presence of ethers.

Alkyl nitrites are formed from the reaction between an alcohol and nitrous acid in aqueous solution according to the following equilibrium:

$$ROH + HNO_2 \underset{}{\overset{K}{\rightleftharpoons}} RONO + H_2O$$

It may be expected that ethers could form O-nitroso species by a similar reaction:

$$ROR + HNO_2 \overset{K}{\rightleftharpoons} RR'ONO^+ + H_2O$$

However there is little or no evidence in support of the formation of O-nitroso cations from ethers. In the present study it was aimed to examine the effect of several ethers upon the nitrosation of N-methylaniline in order to obtain information on the formation of such cations. Reaction conditions were selected such that reactions were of the first order, with the nitrite present in large excess. The

concentrations of reagents were as follows:
$[HClO_4]$ = 3.667 x10^{-2}M, $[NaNO_2]$ = 2.016 x10^{-3}M,
[ether] = ca. 0.18 - 0.24 M, [NMA] = 1.17 x10^{-4}M. Kinetic measurements were made at 31^{o}C by monitoring the appearance of the nitrosamine at 290nm. Rate measurements were made at one ether concentration for each of the four ethers studied. The experimental results are presented in table 3.19.

Table 3.19 Nitrosation of NMA in the presence of ethers.

ether	[ether],M	k_o, s^{-1}
none	0	1.40
monoglyme	0.189	1.45
THF	0.237	1.42
diethylether	0.185	1.54
dioxan	0.225	1.47

The table demonstrates that the addition of ethers (at concentrations used in this study) had no significant effect upon the nitrosation of N-methylaniline. Consequently, no evidence was obtained in support of the proposed formation of O-nitroso cations from ethers and nitrous acid. It is thought that there would be very little of the $RR'ONO^+$ species present, unlike the species $RHONO^+$, since the nitrosyl ether species cannot lose a proton to form a stable O-nitroso compound.

3.5 Nitrosation of p-nitro N-methylaniline in the presence of thiols.

The formation of thionitrites from thiols and nitrosating agents is well known[90]. Stedman and co-workers have demonstrated that cysteine undergoes S-nitrosation in a rapid reaction, the equilibrium constant for the formation of the thionitrite being so large that the reaction is considered to be irreversible[95]. In the present study it was decided to investigate the nitrosation of a secondary amine in the presence of cysteine, penicillamine and other thiols in order to investigate their ability to act as nitrite traps.

p-Nitro N-methylaniline was selected as a suitable amine; reactions could then be followed by monitoring the decrease in absorbance due to the amine at a suitable wavelength (405 or 420nm) and the nitrosamine formation could be seen at 310nm. The concentrations of reagents were as follows: $[NaNO_2] = 3.85 \times 10^{-4}M$, [pNNMA] = $2.88 \times 10^{-5}M$, $[HClO_4] = 3.70 \times 10^{-2}M$.

Two thiols, L-cysteine and N-acetyl (D,L)penicillamine were used in the study. For both thiols, the extent of formation of the nitrosamine showed a great decrease with increasing thiol concentration. Furthermore, it was found that the nitrosamine formation could be completely suppressed by adding sufficient amounts of either cysteine or penicillamine (in ca. 20 fold excess over the amine). In experiments where this limit had not been reached, the yield of nitrosamine was significantly reduced, particularly

if the thiol and nitrous acid solutions were mixed for ca. 45s before adding the amine.

These results indicate that there is direct competition between the thiol and the amine for the nitrous acid (or the nitrosating agent in equilibrium with the nitrous acid) as shown in Scheme 3.

$$2HNO_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} N_2O_3 + H_2O .$$

$$N_2O_3 + pNNMA \xrightarrow{k_2} R'R''NNO^+_N \longrightarrow R'R''NNO$$

$$N_2O_3 + RSH \xrightarrow{k_3} RSNO^+_H \longrightarrow RSNO$$

Scheme 3

According to Scheme 3 and applying the principle of stationary states to the nitrous anhydride, the total rate of disappearance of the nitrous acid is given by equation 3.9, assuming that $k_1 \lesssim k_2[pNNMA]$ and $k_{-1} \gg k_3[RSH]$.

$$\text{rate} = \frac{k_2k_1}{k_{-1}}[HNO_2]^2[pNNMA] + \frac{k_3k_1}{k_{-1}}[HNO_2]^2[RSH] \qquad 3.9$$

In a series of kinetic runs the effect on the rate of disappearance of the p-nitro N-methylaniline of various concentrations was investigated. Kinetic runs were carried out using a large excess of nitrite and under such conditions the rate of disappearance of the amine should be given by equation 3.10

$$\frac{-d[pNNMA]}{dt} = \frac{k_2k_1}{k_{-1}}[HNO_2]^2[pNNMA] \qquad 3.10$$

Since the nitrite concentration will not be constant reactions should not be of the first order. This was found to be the case. The differences between the alkyl nitrite and thionitrite systems are marked and appear to be a result of the difference in the positions of the respective equilibria. The equilibrium constants for the formation of alkyl nitrites in aqueous solution at 25^{o} - $0^{o}C$ are ca. 0.1 to 1.0 l mol^{-1}. However, the equilibrium constants for the formation of thionitrites are several orders of magnitude larger. Indeed for the formation of thionitrites the equilibrium is so far over to the side of the products that it can hardly be classified as an equilibrium and may be considered irreversible. The difference between the alkyl- and thionitrite systems could have been a result of differences in the rate constants for the O- and S-nitrosation reactions. However, these rate constants appear to be comparable in magnitude and so this cannot be the factor responsible for the differences between the two systems.

The effect of two thioethers, methionine and S-methylcysteine, upon the nitrosation of p-nitro N-methyl-aniline was also subject to a preliminary investigation. The formation of the S-nitroso cations have been proposed in several cases, for example in the nitrosation of thiourea[95]. The catalysis of the denitrosation of N-methyl N-nitroso-aniline in aqueous sulphuric acid by methionine and S-methylcysteine in which it is thought that S-nitroso species are formed but are removed rapidly by nitrite traps[101]. In the present study it was found that for very high

concentrations (ca. 750 fold excess over the amine) were required in order to achieve the complete suppression of nitrosamine formation. In the case of methionine the complete suppression of the N-nitrosation was not achieved.

The results for the nitrosation in the presence of the thioethers are satisfactorily explained on the basis of the S-nitrosation reactions. As stated previously, the thionitrite formation was virtually irreversible. However, in the case of the thioethers the equilibrium given in Scheme 4 is established:

$$RSR' + HNO_2 \underset{H^+}{\overset{K}{\rightleftharpoons}} RR'SNO^+_H + H_2O$$

Scheme 4

Unlike the thiols, the S-nitroso cation cannot lose a proton to form a stable, neutral thionitrite and therefore the equilibrium constants for the formation of the S-nitroso species are much smaller than for the thionitrite reactions.

In conclusion, it appears that thiolic species such as cysteine and N-acetyl (D,L) penicillamine are quite effective as nitrite traps but the thioethers are much less efficient. Cysteine is used in the food industry as an additive to prevent discolouration in fruit[118]. It is possible that cysteine could have the potential use as a nitrite trap in order to inhibit nitrosamine formation from the nitrous acid produced from nitrite-preserved foodstuffs.

The direct nitrosation of a thiol (N-acetyl (D,L) penicillamine) is investigated in Chapter 5 of this thesis.

3,6 Experimental.

3.6.1 Reagents.

Commercial samples of N-methylaniline and p-nitro N-methylaniline were obtained. N-methylaniline was purified by reduced pressure distillation and p-nitro N-methylaniline was recrystallised from ethanol. Analytical grade sulphuric acid and sodium nitrite were used. All other reagents were of the highest purity available and were used without further purification. Perchloric acid solutions were prepared by dilution of 62% aqueous perchloric acid and were standardised by titration against sodium hydroxide solutions using phenol red as an indicator.

3.6.2 rate measurements.

All rate measurements were carried out at 31^{o}C in the cell of a Beckman 25 or Pye Unicam SP 8-100 visible-ultraviolet recording spectrophotometer at 405 or 420 nm for pNNMA or at 290nm for NMA.

The procedure for determining rate constants was as follows: a concentrated solution of aqueous sodium nitrite and a solution containing all other reagents (total volume of 25 cm^3) were thermostatted. The reaction was started by adding 1cm^3 of the nitrite to the solution containing all the other reagents and after mixing the contents of the flask, a portion was transferred to a 1cm cuvette and placed in the thermostatted cell holder of the spectrophotometer. The reactions were then monitored by following the disappearance of the amine or, if possible, the appearance of the nitrosamine.

Reactions were carried in the presence of a large excess of sodium nitrite so that reactions were generally of the first order. The first order rate constants, k_o, defined by

$$-\frac{d[\text{amine}]}{dt} = k_o[\text{amine}]$$

were calculated either by plots of $\ln[A_\infty - A_t]$ or $\ln[A_t - A_\infty]$ against time or by means of the Guggenheim method[119] in those cases where side reactions prevented infinity absorbance measurements from being made.

CHAPTER FOUR

REACTIONS INVOLVING ALKYL NITRITES IN ALCOHOL SOLVENT.

4,1 Reactions of n-propyl nitrite in n-propanol.

4,1,1, Introduction.

Although alkyl nitrites have been widely used as nitrosating agents few mechanistic studies have been made on their heterolytic reactions. There are, to my knowledge, no reports in which it has been shown beyond reasonable doubt whether alkyl nitrites act as direct or indirect nitrosating agents. Shenton and Johnson have reported behaviour as indirect nitrosating agents in the reaction between cyclohexyl nitrite and sulphanilamide in aqueous acidic conditions[87]. They compared the diazotisation of sulphanilamide with cyclohexyl nitrite and nitrous acid in aqueous sulphuric acid. The concentration of product formed at various times throughout the reaction were determined by coupling the diazonium ion with 1-naphthol to form an azo dye which absorbed at 470nm. For reactions of nitrous acid and the alkyl nitrite the kinetics were found to be identical.

The direct behaviour of certain alkyl nitrites (those possessing β-electron withdrawing substituents) has been reported for their reaction with secondary amines in basic conditions.[81]

In the present work it was decided to make a study of reactions in non-aqueous conditions using an alkyl nitrite as a nitrosating agent in order to establish how alkyl nitrites act as nitrosating agents. n-Propyl nitrite was selected as a suitable alkyl nitrite and n-propanol was used as the solvent. The substrates selected were aniline, N-methylaniline and p-nitroaniline; aniline and N-methylaniline were selected as an example of a

diazotisation reaction and an N-nitrosation reaction; p-nitroaniline was selected as an example of a reaction with a much less basic amine.

4.1.2. The halide ion and thiourea catalysed reaction.

For reactions in n-propanol acidified with sulphuric acid in the absence of added nucleophiles there was no significant reaction for aniline or N-methylaniline. For example, in a solution of 0.14M sulphuric acid in n-propanol (a considerably higher acidity than used in other experiments) containing 1.53×10^{-4}M n-propyl nitrite and 4.5×10^{-3}M N-methylaniline the observed first order rate coefficient was ca. 4.0×10^{-5} s^{-1}. However, upon the addition of nucleophiles such as chloride ion, bromide ion and thiourea the reaction proceeded quite rapidly.

Halide ions catalyse nitrosation reactions by forming the corresponding nitrosyl halides which are the effective nitrosating agents. It has recently been shown that thiourea is an effective catalyst towards reactions involving N-nitrosation[35]; its mode of action involves the formation of the S-nitroso cation which then acts as a nitrosating agent.

In the present study reactions were carried out at 31°C in n-propanol acidified with sulphuric acid containing lithium chloride, tetraethylammonium chloride, lithium bromide or thiourea. Some reactions were also carried out in n-propanol containing dissolved hydrogen chloride. Reaction conditions were such that the amine was always

present in large excess over the propyl nitrite so that reactions were of the first order. Rate constants were determined by monitoring the change in absorbance due to the diazonium ion or the N-methyl N-nitrosoaniline at a suitable wavelength. The observed first order rate constant, k_o, defined by:

$$\frac{d[\text{product}]}{dt} = k_o[\text{nPrONO}]$$

was shown to be independent of the initial n-propylnitrite concentration; this is demonstrated by the results in Table 4,1.

Table 4.1 dependence of k_o upon $[\text{nPrONO}]_i$

$[\text{nPrONO}]_i \times 10^4$, M	$k_o \times 10^3$, s^{-1}
0.75	10.9
1.49	10.8
2.99	10.6

$[\text{aniline}] = 2.08 \times 10^{-3}$ M
$[\text{HCl}] = 7.54 \times 10^{-2}$ M

The observed first order rate constant has also been shown to have a first order dependence upon the concentration of each of the amines studied; the data for the variation of k_o with the amine concentration are presented in tables 4.2 4.3 and 4.4. The data for aniline are also presented in figure 1.

The dependence of k_o on the concentrations of added chloride ion, bromide ion and thiourea has also been investigated. It was also intended to examine the dependence

Table 4.2 dependence of k_o upon [aniline].

[aniline] $x10^3$,M	k_o $x10^2$, s^{-1}
2.08	1.02
3.12	1.60
4.16	2.00
5.19	2.48
6.23	3.18

[nPrONO] = 1.49 x 10^{-4}M

[HCl] = 7.54 $x10^{-2}$M

Table 4.3 dependence of k_o upon [N-methylaniline]

[NMA] $x10^3$,M	k_o $x10^3$,s^{-1}
1.86	6.10
3.73	10.8
5.59	14.9

[nPrONO] = 1.36 x 10^{-4}M

[H_2SO_4] = 3.50 x 10^{-2}M

[LiBr] = 2.19 x 10^{-3}M

Table 4.4 dependence of k_o upon [p-nitroaniline]

[pNA] $x10^4$M	k_o $x10^3$, s^{-1}
4.40	0.92
6.0	1.54
8.80	1.89
13.21	3.09

[nPrONO] = 7.65 x 10^{-5}M

[H_2SO_4] = 2.38 $x10^{-2}$M

[LiBr] = 3.31 $x10^{-2}$M

on the concentrations of thiocyanate ion and iodide ion, but the study of these reactions was prohibited by difficulties due to the insolubility of the salts and side reactions.

At low nucleophile concentrations, graphs of k_o against the nucleophile concentration were linear but at higher concentrations k_o was found to level-off and eventually became independent of the nucleophile concentration. The dependence of k_o upon the added nucleophile concentration for each amine are shown in tables 4.5 to 4.13 and in figures 1 and 2.

Dependence of k_o upon [chloride ion].

Table 4.5 diazotisation of aniline

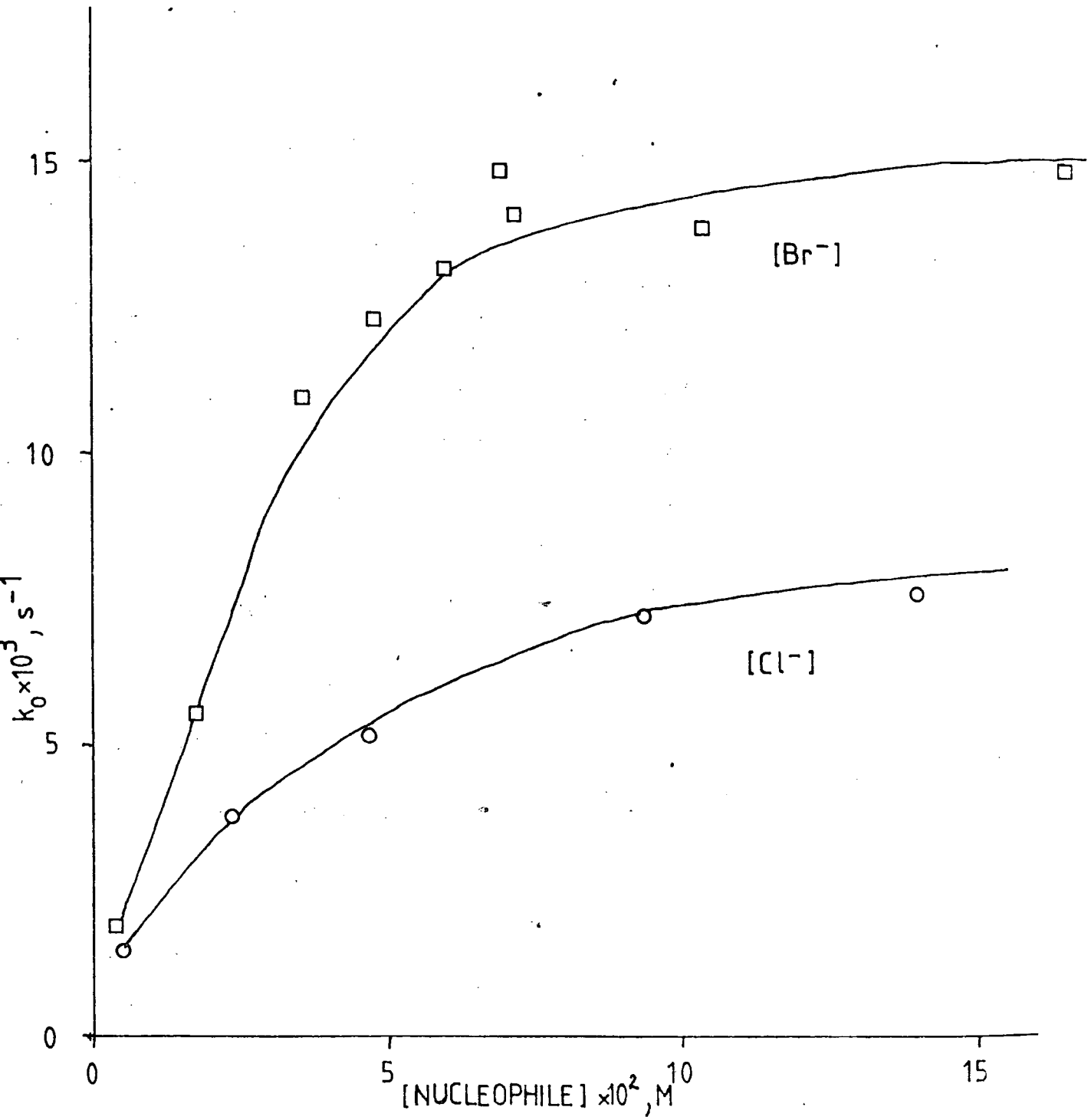
$[Cl^-]$ x10^2,M	k_o x10^3, s^{-1}
0.48	1.53
2.34	3.81
4.67	5.18
9.35	7.24
14.02	7.54

$[nPrONO] = 1.36 \times 10^{-4}M$

$[H_2SO_4] = 3.46 \times 10^{-2}M$

$[aniline] = 1.93 \times 10^{-3}M$

FIGURE 1 - DIAZOTISATION OF ANILINE;
CATALYSIS BY NUCLEOPHILES



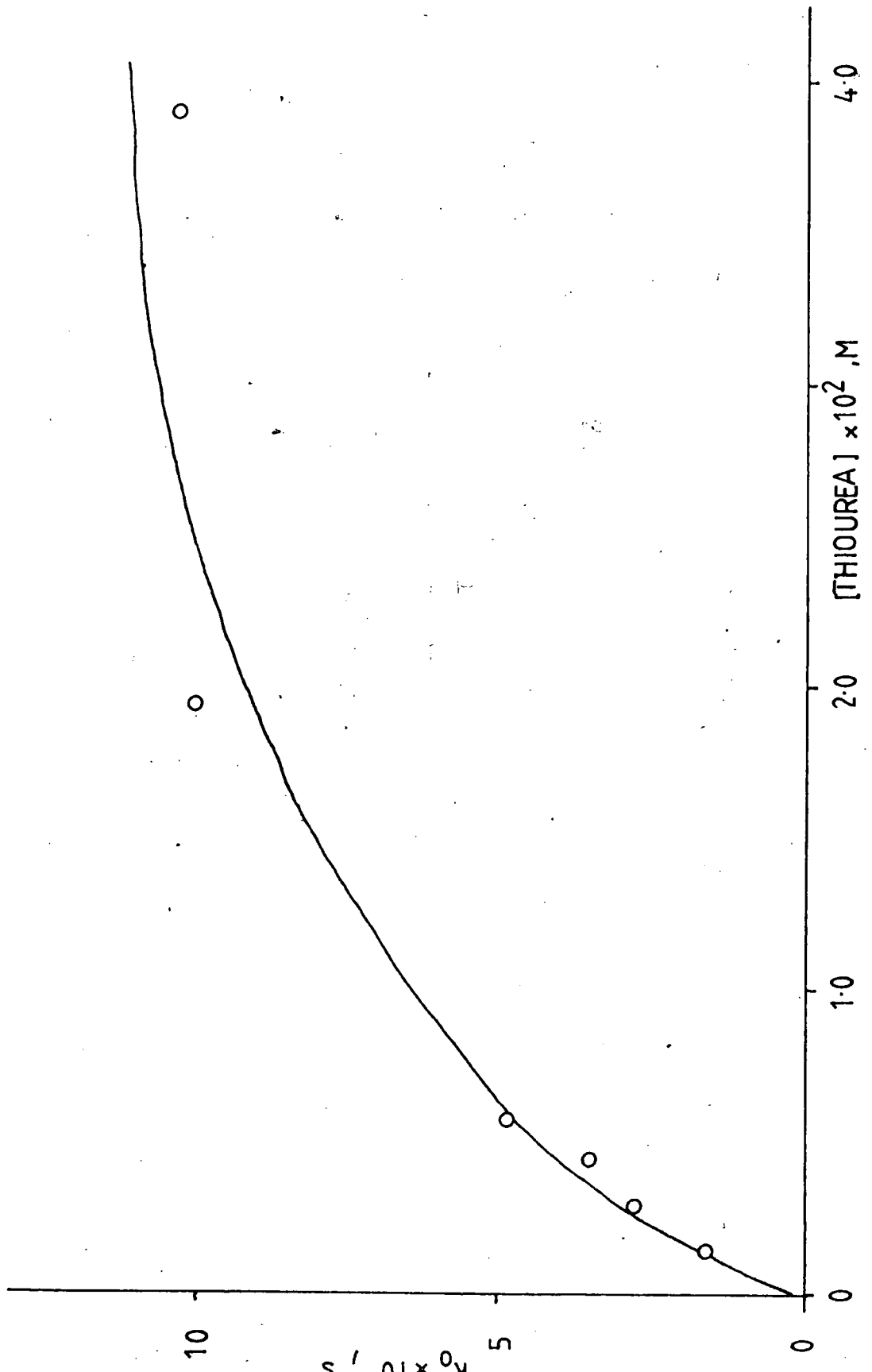


FIGURE 2 - NITROSATION OF NMA; CATALYSIS BY THIOUREA.

Table 4.6 nitrosation of N-methylaniline

$[Cl^-]$ x10^2, M	k_o x10^3, s^{-1}
0.34	4.77
0.95	9.73
1.71	15.93
2.56	19.99
3.41	22.87

$[nPrONO] = 1.36 \times 10^{-4}M$

$[H_2SO_4] = 3.46 \times 10^{-2}M$

$[NMA] = 1.50 \times 10^{-3}M$

Table 4.7 nitrosation of NMA at low [chloride ion]

$[Cl^-]$ x10^3, M	k_o x10^3, s^{-1}
0.95	1.14
1.89	3.03
2.52	3.94
3.79	5.54

$[nPrONO] = 1.36 \times 10^{-4}M$

$[H_2SO_4] = 3.46 \times 10^{-2}M$

$[NMA] = 1.43 \times 10^{-3}M$

Table 4.8 diazotisation of p-nitroaniline

$[Cl^-]$ x10^2M	k_o x10^3, s^{-1}
1.16	1.03
1.93	1.49
3.86	2.23
5.79	2.62
7.72	3.47

continued overleaf..

9.65	3.35
14.48	3.50

$[nPrONO] = 7.65 \times 10^{-5}M$

$[H_2SO_4] = 2.38 \times 10^{-2}M$

$[pNA] = 8.38 \times 10^{-4}M$

Dependence of k_o upon [bromide ion]

Table 4.9 diazotisation of aniline

$[Br^-] \times 10^2, M$	$k_o \times 10^3, s^{-1}$
0.35	1.91
1.73	5.53
3.58	10.94
4.77	12.24
5.96	13.17
6.92	14.82
7.15	14.08
10.38	13.80
15.50	14.78

$[nPrONO] = 1.36 \times 10^{-4}M$

$[H_2SO_4] = 3.43 \times 10^{-2}M$

$[aniline] = 1.97 \times 10^{-3}M$

Table 4.10 nitrosation of N-methylaniline

$[Br^-]$ $x10^3$,M	k_o $x10^3$,s^{-1}
1.09	2.39
2.19	4.35
3.29	6.11
10.96	15.90
21.92	22.80
32.88	27.15

$[nPrONO] = 1.36 \times10^{-4}M$

$[H_2SO_4] = 3.46 \times10^{-2}M$

$[NMA] = 1.50 \times10^{-3}M$

Table 4.11 diazotisation of p-nitroaniline

$[Br^-]$ $x10^2$,M	k_o $x10^3$,s^{-1}
0.99	0.94
1.65	1.37
3.31	2.27
4.96	2.51
6.61	2.76
8.29	2.71
16.58	3.43

$[nPrONO] = 7.65 \times10^{-5}M$

$[H_2SO_4] = 2.38 \times10^{-2}M$

$[pNA] = 8.38 \times10^{-4}M$

Table 4.12 diazotisation of aniline

[thiourea] $x10^2$,M	k_o $x10^3$,s^{-1}
1.00	2.42
2.00	3.14
3.00	3.99
4.00	4.10
5.00	4.73
6.00	4.59

[nPrONO] = 2.35 $x10^{-4}$M

$[H_2SO_4]$ = 3.46 $x10^{-2}$M

[aniline] = 4.14 $x10^{-3}$M

Table 4.13 nitrosation of N-methylaniline

[thiourea], $x10^3$,M	k_o $x10^3$, s^{-1}
1.44	1.64
2.88	2.80
4.33	3.52
5.77	4.90
19.46	10.11
38.94	10.35

[nPrONO] = 1.36 $x10^{-4}$M

$[H_2SO_4]$ = 3.46 $x10^{-2}$M

[NMA] = 1.49 $x10^{-3}$M

One would expect the reaction to be catalysed by nucleophiles if the nitrosyl halide (or S-nitroso thiourea complex) were formed by the reaction of the nucleophile and the n-propyl nitrite and the nitrosyl halide was the effective nitrosating agent. This reaction (equation 4.1) is

analogous to the formation of the nitrosyl halide from nitrous acid.

$$RONO + H^+ + X^- \rightleftharpoons ROH + NOX \qquad 4.1$$

The levelling-off of the dependence of k_o on the nucleophile concentration at high [nucleophile] may be rationalised by considering the magnitude of the equilibrium constant, K_{NOX}, for equation 4.1. If K_{NOX} were sufficiently large then at high nucleophile concentrations the nitrosyl halide [or S-nitroso thiourea complex] would be formed almost quantitatively. If this is the case then the inequality

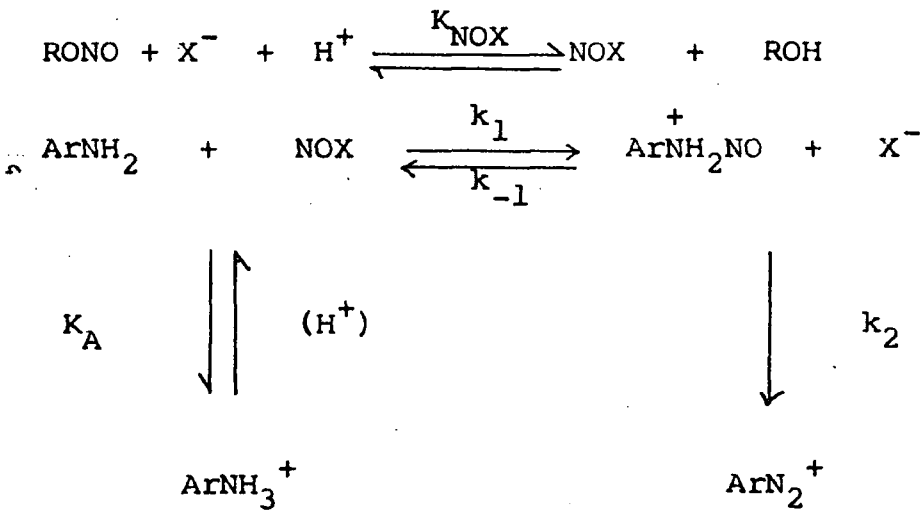
$$(K_{NOX}[H^+][Cl^-])^{-1} << 1$$

should apply. The values of K_{NOX} have been determined for the nitrous acid reactions in water at 25°C to be $1.1 \times 10^{-3}\ l^2 mol^{-2}$ and $5.1 \times 10^{-2}\ l^2 mol^{-2}$ for nitrosyl chloride[27] and nitrosyl bromide[28] respectively; they are known to be larger in glacial acetic acid[78] and acetic acid-carbon tetrachloride solvent mixtures[79]. Woppmann and co-workers have reported values of K_{NOX} in methanol at 0°C to be $5 \times 10^{-2}\ l^2 mol^{-2}$ (for nitrosyl chloride)[39] and $2.0 \times 10^{-2}\ l^2 mol^{-2}$ (for nitrosyl bromide)[82]

In the present work, allowing for temperature differences and the change in solvent from methanol to n-propanol, it seems that for the selected acid, chloride ion and bromide ion concentrations the previously stated inequality does not apply. In support of this, no spectroscopic evidence of the nitrosyl halides was found in these reaction conditions. It appears, therefore, that the

levelling-off of the dependence of k_o on the nucleophile concentration is not due to the quantitative formation of the nitrosyl halides and so an alternative explanation must be found.

Woppmann has established that in methanolic solutions of hydrogen chloride[39] and hydrogen bromide[82] the diazotisation of aniline involves reversible N-nitrosation by the nitrosyl halide as outlined in Scheme 4.1 below:



Scheme 4.1

The same situation has been found to apply to diazotisation involving nitrosyl halides in aqueous solutions[32], especially for the diazotisation of substrates which posess electron withdrawing substituents on the aromatic ring. For reactions in n-propanol the reversibility of the nitrosation stage would not be unexpected; such a process would be quite consistent with observations made on the dependence of k_o on the nucleophile concentration.

The denitrosation of the primary nitrosaminium cation is analogous to the denitrosation of N-nitrosamines, a reaction which has been studied in depth in aqueous[34,51] and alcoholic solutions[61]. Denitrosation has been shown to occur more rapidly in ethanol than in water and also more rapidly for substrates bearing electron-withdrawing substituents on the aromatic ring[120].

In aqueous solutions of dilute acids, diazotisation and nitrosation of amines involves the reaction of the free base rather than its protonated form and it is not unreasonable to assume that for reactions in n-propanol solvent reaction also takes place via the unprotonated amine. In the case of the reactions involving aniline and N-methylaniline the total amine concentration would be approximately equal to that of the protonated amine since the pK_{BH^+} values of these amines in water are 4.6 and 4.85 respectively[121]. Assuming that the reactions occur according to Scheme 4.1 it is possible to deduce an expression for k_o in terms of the rate constants k_1, k_{-1} and k_2:

the acid dissociation constant, K_A, of the protonated amine is defined as:

$$K_A = \frac{[H^+][A]}{[AH^+]} = \frac{[H^+][A]}{[A]_T}$$

where $[A]_T$ = [total amine]

the equilibrium constant, K_{NOX}, for the formation of the nitrosyl halide from n-propyl nitrite is defined:

$$K_{NOX} = \frac{[NOX]}{[RONO][H^+][X^-]} = \frac{[NOX]}{[RONO]_T[H^+][X^-]}$$

the rate of reaction in Scheme 4.1 is given by equation 4.2

$$\text{rate} = k_2[\overset{+}{\text{ArNH}_2\text{NO}}] \qquad 4.2$$

applying the principle of stationary states to the protonated N-nitroso intermediate:

$$\frac{d[\text{ArNH}_2\text{NO}^+]}{dt} = 0 = k_1[\text{NOX}][\text{ArNH}_2] - k_{-1}[\text{ArNH}_2\text{NO}^+][X^-] - k_2[\overset{+}{\text{ArNH}_2\text{NO}}]$$

$$[\text{ArNH}_2\text{NO}^+] = \frac{k_1[\text{NOX}][\text{ArNH}_2]}{k_{-1}[X^-]+k_2}$$

substituting for [NOX], [$ArNH_2$] and [$ArNH_2NO^+$] in the rate expression 4.2 leads to equation 4.3

$$\text{rate} = \frac{k_2k_1K_{NOX}K_A[X^-][\text{RONO}]_T[A]_T}{k_{-1}[X^-] + k_2} \qquad 4.3$$

the first order observed rate constant, k_o, is defined

$$\text{rate} = k_o[\text{RONO}]_T \qquad 4.4$$

and hence k_o may be expressed by equation 4.5

$$k_o = \frac{k_2k_1K_{NOX}K_A[X^-][A]_T}{k_{-1}[X^-] + k_2} \qquad 4.5$$

From equation 4.5 it is clear that two limiting conditions should be observed when either of the following inequalities hold:

$$k_{-1}[X^-] \ll k_2$$

$$k_{-1}[X^-] \gg k_2$$

In the first case the observed rate constant would show a first order dependence on [nucleophile] since the expression for k_o would be reduced to equation 4.6

$$k_o = k_1K_{NOX}K_A[X^-][A]_T \qquad 4.6$$

If the second case were applicable (at high [nucleophile]) then k_o would be independent of the nucleophile concentration.

The reciprocal of equation 4.5 is given in equation 4.7.

$$\frac{1}{k_o} = \frac{1}{k_1 K_{NOX} K_A [X^-][A]_T} + \frac{k_{-1}}{k_1 k_2 K_{NOX} K_A [A]_T} \qquad 4.7$$

From this equation it is indicated that a plot of $(k_o)^{-1}$ against $([X^-])^{-1}$ should be linear across the whole range of nucleophile concentrations. Moreover, from such graphs the ratio of the slope to the intercept should give the ratio of the rate constants k_2 to k_{-1}. The data for the variation of $(k_o)^{-1}$ to $([\text{nucleophile}])^{-1}$ are presented in tables 4.14 to 4.21. Some of the data are also illustrated in figures 3, 4 and 5. The values of the ratio k_2/k_{-1} are given in table 4.22.

Table 4.14 Variation of $(k_o)^{-1}$ with $([Cl])^{-1}$ for the diazotisation of aniline.

$([Cl^-])^{-1}$, l mol^{-1}	k_o^{-1}, s
7.14	133
10.7	138
21.4	193
42.8	262
214	655

slope = 3.73 $\pm$ 0.28 mol l^{-1}s

intercept = 105 $\pm$ 7 s

Table 4.15 chloride ion catalysed nitrosation of NMA

$([Cl^-])^{-1}$, l mol^{-1}	$(k_o)^{-1}$, s
29.3	43.7
39.1	50.0
58.6	62.8
106	103
293	210

slope = 0.630 ± 0.002 mol l^{-1}s

intercept = 25.49 ± 0.24 s

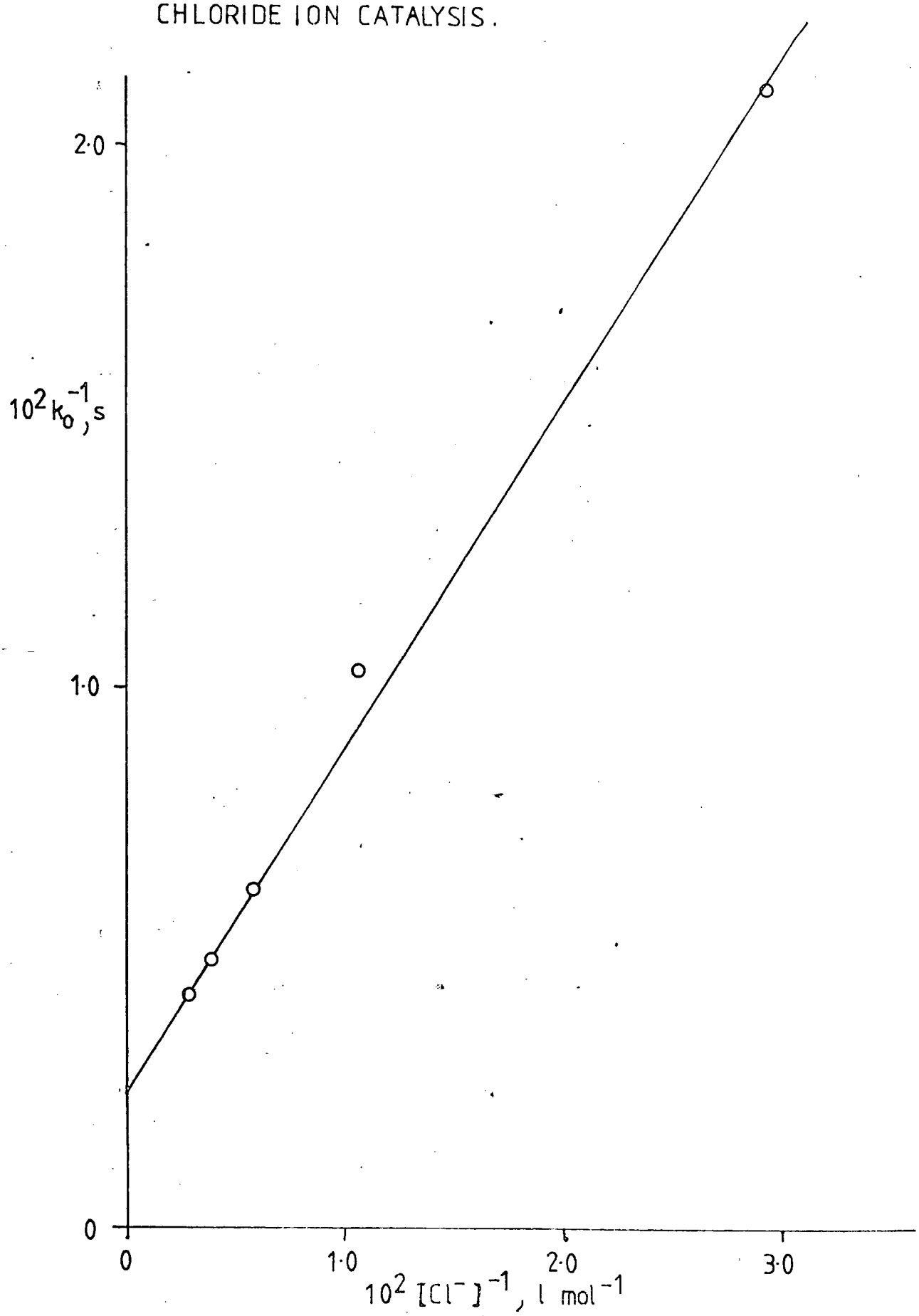
Table 4.16 chloride ion catalysed diazotisation of p-nitroaniline.

$([Cl^-])^{-1}$, l mol^{-1}	$(k_o)^{-1}$, s
6.9	286
10.4	299
12.9	288
17.3	382
25.9	448
51.8	672
86.4	970

slope = 8.57 ± 0.05 mol l^{-1}s

intercept = 229 ± 3 s

FIGURE 3 - NITROSATION OF NMA, CHLORIDE ION CATALYSIS.



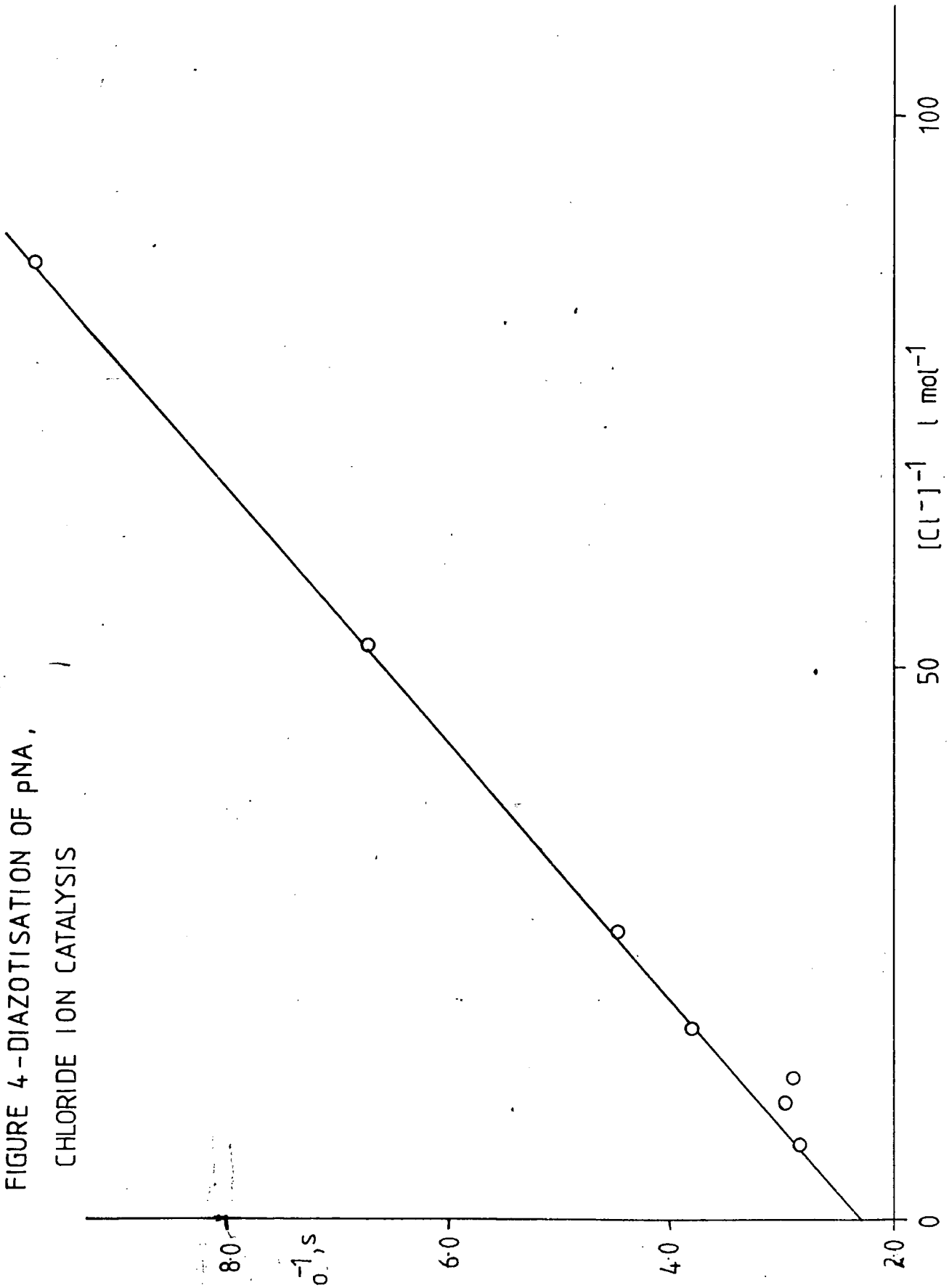


FIGURE 4 - DIAZOTISATION OF pNA, CHLORIDE ION CATALYSIS

FIGURE 5 - DIAZOTISATION OF ANILINE; THIOUREA CATALYSIS

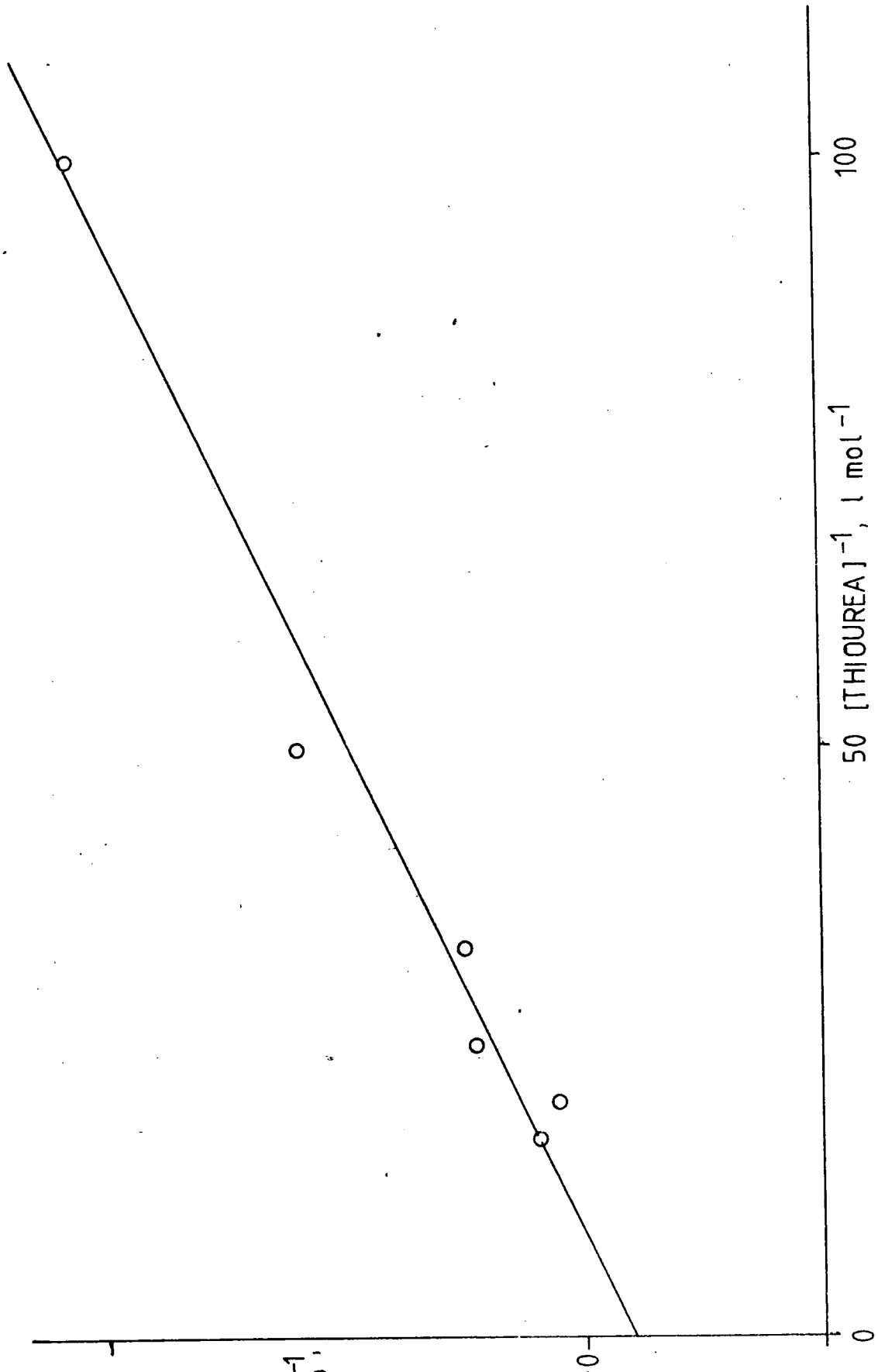


Table 4.17 bromide ion catalysed diazotisation of aniline

$([Br^-])^{-1}$, l mol^{-1}	$(k_o)^{-1}$, s
4.3	59.4
6.5	67.5
9.6	72.5
14.0	71.0
14.4	67.5
16.8	75.9
21.0	82.0
28.0	91.4
57.7	181
289	523

slope = 1.64 $\pm$ 0.05 mol l^{-1}s

intercept = 53.4 $\pm$ 4.7 s

Table 4.18 bromide ion catalysed nitrosation of NMA

$([Br^-])^{-1}$, l mol^{-1}	$(k_o)^{-1}$, s
30.4	36.8
45.6	43.8
91.2	62.8
304	164
450	230
912	419

slope = 0.436 $\pm$ 0.008 mol l^{-1}s

intercept = 26.1 $\pm$ 3.3 s

Table 4.19 bromide ion catalysed diazotisation of p-nitroaniline

$([Br^-])^{-1}$, l mol^{-1}	$(k_o)^{-1}$, s
6.0	292
12.1	369
15.1	362
20.2	399
30.2	441
60.6	732
101	1059

slope = 8.01 $\pm$ 0.16 mol l^{-1} s

intercept = 250 $\pm$ 8 s

Table 4.20 thiourea catalysed diazotisation of aniline

$([thiourea])^{-1}$ l mol^{-1}	$(k_o)^{-1}$, s
16.7	218
20.0	211
25.0	244
33.3	250
50.0	318
100	413

slope = 2.33 $\pm$ 0.10 mol l^{-1}s

intercept = 180 $\pm$ 5 s

Table 4.21 thiourea catalysed nitrosation of NMA

$([\text{thiourea}])^{-1}$ $1\ mol^{-1}$	$(k_o)^{-1}$, s
25.7	96.6
51.4	98.9
173	204
231	284
347	357
693	610

slope = 0.785 ± 0.042 mol $l^{-1}s$

intercept = 76.0 ± 15.4 s

Table 4.22 k_2/k_{-1} values for diazotisation and N-nitrosation.

nucleophile	aniline	NMA	pNA
Cl^-	0.037	0.025	0.037
Br^-	0.033	0.021	0.032
thiourea	0.013	0.010	-

It can be seen that the values of (k_2/k_{-1}) show very little difference, but for a given amine the ratio decreases in the sequence:

$$Cl^- > Br^- > \text{thiourea}$$

This sequence is just that which would be expected from the consideration of the nucleophilicities of the catalysts. The decrease in the ratio with increasing nucleophilicity

would be expected since an increase in the nucleophilicity would result in an increase in the value of k_{-1} but would not have any effect upon the value of k_2 because k_2 should be independent of the catalyst. However, the magnitude of the decrease is quite small, indicating that the denitrosation process is very rapid and so is not very sensitive to the nature of the nucleophile. The large magnitude of k_{-1} is not totally unexpected since the reaction has to compete with the rapid step having the rate constant k_2. The latter step involves processes such as proton transfers and so would be expected to be rapid.

Both N-methylaniline and aniline show the same type of dependence on the concentrations of added nucleophiles. For the nitrosation of NMA the only process in the stage with rate constant k_2 is the transfer of a proton from the protonated nitrosamine to the solvent. Since aniline shows the same dependence on the nucleophile it therefore appears reasonable to suppose that proton transfer to the solvent is the kinetically important step in the aniline reaction, although further proton transfer reactions together with the loss of a water molecule are also involved.

4.1.3 The effect of changing acidity.

The expression for the first order rate constant, k_o, given in equation 4.5 does not involve the acid concentration and therefore diazotisation and nitrosation of the more basic amines by n-propyl nitrite in n-propanol would not be expected to be subject to acid catalysis. Hence, for the

reactions of aniline and N-methylaniline k_o values should be independent of the acidity. Tables 4.23 and 4.24 demonstrate the effect of changing the acidity on k_o for aniline and N-methylaniline.

The data for NMA clearly demonstrate that for the acidity range considered, k_o is independent of the acidity within the limits of experimental error. However, the data for aniline show a small but steady decrease in k_o with increasing acidity. This effect is outside the limits of experimental error but it is not clear how such an effect could arise, in particular when the results for N-methylaniline showed no such dependence. Even so, it may be said, to a first approximation, that the rate constant k_o is independent of the acidity over the acidity range studied for the reactions of aniline and N-methylaniline.

Table 4.23 variation of k_o with acidity for the nitrosation of NMA.

$[H_2SO_4]$ $x10^2$,M	k_o $x10^2$,s^{-1}
1.75	3.28
3.50	3.20
7.00	3.34
10.5	3.45

$[NMA] = 1.70 \times 10^{-3}$,M

$[Br^-] = 3.48 \times 10^{-2}$M

$[nPrONO] = 1.36 \times 10^{-4}$,M

Table 4.24 Variation of k_o with acidity for the diazotisation of aniline

$[H_2SO_4]$ x10^2,M	k_o x10^2,s^{-1}
1.90	14.1
3.81	12.1
5.71	11.7
7.61	11.2
9.52	11.0

$[aniline] = 2.92 \times 10^{-3}M$

$[Br^-] = 4.14 \times 10^{-2}M$

$[nPrONO] = 1.36 \times 10^{-4}M$

However, on consideration of the diazotisation of p-nitroaniline one would expect to make quite different observations concerning the dependence of k_o on the acidity. p-Nitroaniline is much less basic than either aniline or N-methylaniline and for the acidity range used in the present experiments there would be significant concentrations of the free amine; this was confirmed by the acidic solutions of the amine showing the characteristic yellow colour of the free p-nitroaniline. In the case of the less basic amine, an additional term must be included in the rate expression so that the expression for k_o is now given by equation 4.7.

$$k_o = \frac{k_2 k_1 K_{NOX}[A]_T[H^+](1 + \frac{[H^+]}{K_A})^{-1}}{k_{-1}[X^-] + k_2} \qquad 4.7$$

According to equation 4.7 acid catalysis would be expected for the less basic amines. However, for amines such as aniline and N-methylaniline the inequality

$$1 << \frac{[H^+]}{K_A}$$

holds and so the expression of k_o reduces to equation 4.5 and acid catalysis would not be observed.

For the diazotisation of p-nitroaniline the variation of k_o with changing acidity has been studied and the results are presented in table 4.25

Table 4.25 dependence of k_o on acidity for the diazotisation of p-nitroaniline

$[H_2SO_4]$ x10^2,M	k_o x10^3,s^{-1}
2.39	2.70
4.77	4.03
7.15	5.84
9.54	7.50

$[Br^-] = 8.29 \times 10^{-2}$M

[pNA] = 8.38×10^{-4}M

[nPrONO] = 7.65×10^{-4}M

Clearly, the reaction is acid catalysed. The pK_A value for p-nitroaniline is 1.1 in aqueous solution[121] and in n-propanol I have determined the pK_A of p-nitroaniline to be approximately 0.9 which would give a value of $[H^+]/K_A$ to be about 0.2; significant acid catalysis would therefore be expected. On plotting a graph of k_o against the sulphuric acid concentration it may be seen that there is a linear correlation. However, the data for the hydrogen ion concentration in n-propanol are not available.

It would be of great interest to calculate the values of the rate constants, k_1, for the nitrosation of the amine

by n-propyl nitrite. However, these values are not available since the exact values of the equilibrium constants K_A and K_{NOX} have not been determined in n-propanol solvent. The values of the rate constant, k_1, would have been of interest concerning the subject of encounter controlled reactions. Using the values of K_{NOX} and K_A in water at 25°C then for the diazotisation of aniline and the N-nitrosation of N-methylaniline by nitrosyl bromide under conditions where it was assumed that $k_{-1}[X^-] \ll k_2$, the rate constants k_1 were estimated to be 9 $\times 10^8$ l mol^{-1} s^{-1} and 7.7 $\times 10^8$ l mol^{-1} s^{-1}. At 25°C a diffusion controlled process involving two neutral species would have a rate constant of ca. 7.9 $\times 10^9$ l mol^{-1} s^{-1}. It appears that the reactions of aniline and N-methylaniline appear to be approaching this limit. In water, aniline and those aniline derivatives containing electron-releasing groups diazotisation via NOCl and NOBr have rate constants which are near to those expected for reaction upon encounter[32]. However, for anilines bearing electron withdrawing groups, rate constants are considerably less than for reaction upon encounter. Similarly, in methanol solvent, it has been reported that rate constants are ca. 10^2 less than expected for a diffusion controlled process[39]. It would be expected that the diazotisation and nitrosation by n-propyl nitrite in n-propanol could have rate constants approaching the diffusion controlled limit.

4.1.4 dependence of k_o on the substrate concentration.

As stated previously, k_o showed a good linear dependence upon the concentration of each of the three amines. It may have been expected that at high amine concentrations the denitrosation of the n-propyl nitrite may become rate limiting as has been observed for reactions in water involving nitrosyl bromide[122] and nitrosyl iodide[123]. However, for the range of amine concentrations studied the dependence of k_o upon the amine concentration was strictly linear, indicating that the limiting case had not been reached.

Alternatively, it was thought that the limiting case could perhaps be achieved by using more reactive substrates, such as hydrazoic acid, hydrazine, sulphamic acid or ascorbic acid. In the present study, attempts to measure rates of nitrosation for these substrates have been made. In the first three cases the insolubility of the corresponding salts in n-propanol prevented these experiments from being performed. In the case of ascorbic acid, the reactions were observed but were of a complex order and detailed kinetic investigations were not made.

4.2 Formation of methyl nitrite in methanol solvent.

4.2.1 Introduction.

In this section of this thesis it was aimed to make a study of the kinetics of the formation of methyl nitrite in methanol solvent. Reactions were rapid and the technique of stopped flow spectrophotometry was employed in the determination of the observed first order rate constants.

4.2.2 the acid catalysed reaction.

The formation of methyl nitrite in the absence of added nucleophiles was conveniently studied by mixing equal amounts of methanolic solutions of sulphuric acid and sodium nitrite in the cell of the stopped-flow spectrophotometer at 25°C. The first order rate constants, defined by:

$$\frac{d[MeONO]}{dt} = k_o[HONO]$$

were found to be dependent upon the concentration of sulphuric acid after making allowance for the removal of acid by the protonation of the nitrite ion. The results are demonstrated in table 4.26 and are illustrated in figure 6.

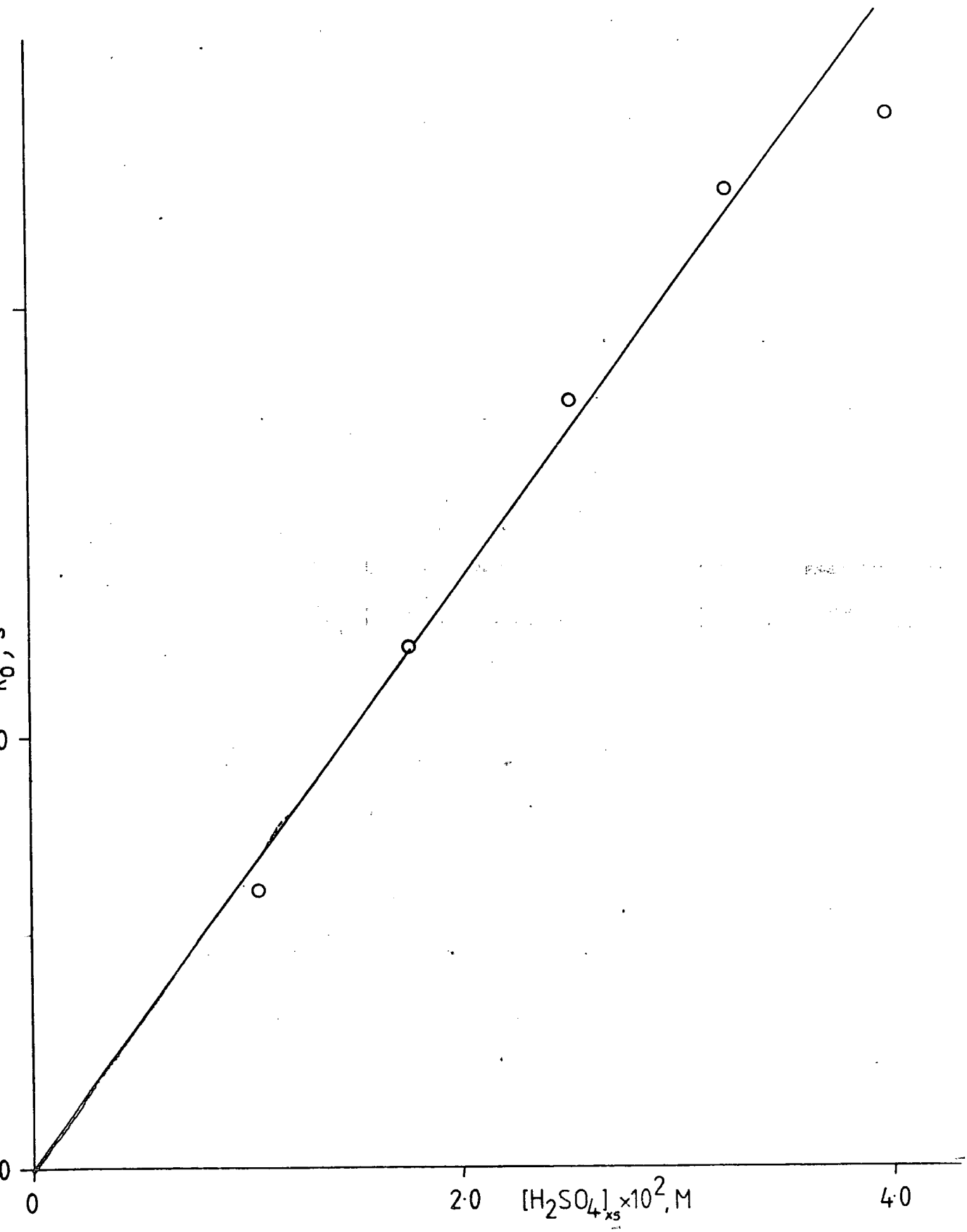
It can be seen that the graph of k_o against the excess sulphuric acid concentration is a reasonable straight line with zero intercept and a slope of $(6.43 \pm 0.62)\ x10^{-3}$ $l\ mol^{-1}\ s^{-1}$. The data for the hydrogen ion concentration in methanol are not available and so further investigation is not possible.

Table 4.26 catalysis of methyl nitrite formation by sulphuric acid.

$[H_2SO_4]_{added}$ $x10^2$, M	$[H_2SO_4]_{xs}$ $x10^2$, M	k_o, s^{-1}
1.46	1.06	6.40 ± 0.32
2.19	1.76	12.14 ± 0.46
2.92	2.52	17.81 ± 0.45
3.65	3.25	22.74 ± 0.77
4.38	3.98	24.58 ± 0.47

$[NaNO_2] = 8.02\ x10^{-3}M$

FIGURE 6 - ACID CATALYSIS OF METHYL NITRITE FORMATION.



4.2.3 The halide ion catalysed reaction.

The formation of methyl nitrite in the presence of halide ions is studied at 0°C in this section of work.

The first order nature of the reaction was demonstrated by observing the effect on k_o of changing the nitrite concentration. Good first order plots were obtained and after making allowance for the slight change in the acidity when using different nitrite concentrations the first order rate coefficient was shown to be independent of the nitrite concentration (table 4.27).

Table 4.27 dependence of k_o on the nitrite concentration.

$[NaNO_2]$ $x10^2$, M	$[H^+]_{xs}$ $x10^2$, M	k_o s^{-1}	$k'(=k_o/[H^+]_{xs})$ $l\ mol^{-1}s^{-1}$
0.61	5.47	4.61±0.09	84.2± 1.6
1.22	4.85	4.21±0.15	86.8±3.1

For the formation of methyl nitrite in methanolic hydrogen chloride the variation of k_o with the hydrogen ion concentration was investigated. The results are presented in table 4.28. Since the acidity function for sulphuric acid in pure methanol does not appear to have been established the acid catalysis of the reaction could alternatively be studied using hydrogen chloride. However the use of hydrogen chloride provides other complications - chloride ion catalysis.
A graph of k_o against the excess hydrogen chloride concentration gave a good linear plot with a slope of $(1.186 \pm 0.044)\ x10^{-2}\ l\ mol^{-1}\ s^{-1}$ and zero intercept. This

indicates that k_o is proportional to the hydrogen ion concentration:

$$k_o = k_1[H^+] \qquad 4.8$$

Table 4.28 dependence of k_o on [hydrogen chloride]

$[HCl]\ x10^2$,M	$[HCl]_{xs}\ x10^2$,M	k_o, s^{-1}
4.70	3.83	4.13 ± 0.13
5.88	5.01	5.56 ± 0.20
7.05	6.18	6.71 ± 0.33
8.22	7.35	7.78 ± 0.12
9.40	8.53	9.75 ± 0.22
11.75	10.88	12.50 ± 0.59

$[NaNO_2] = 8.66\ x10^{-3}M$

The catalysis by chloride ion and bromide ion at 0°C has also been investigated and the results are given in tables 4.29 and 4.30. In both cases the initial sodium nitrite concentration was 0.010M and the lithium halides were used.

Table 4.29 methyl nitrite formation; catalysis by chloride ions.

[LiCl],M	[total chloride] M	k_o, s^{-1}
0	0.061	5.54± 0.18
0.122	0.183	5.58 ± 0.37
0.486	0.547	6.14 ± 0.22
0.729	0.790	6.03 ± 0.23
0.973	1.034	6.57 ± 0.32

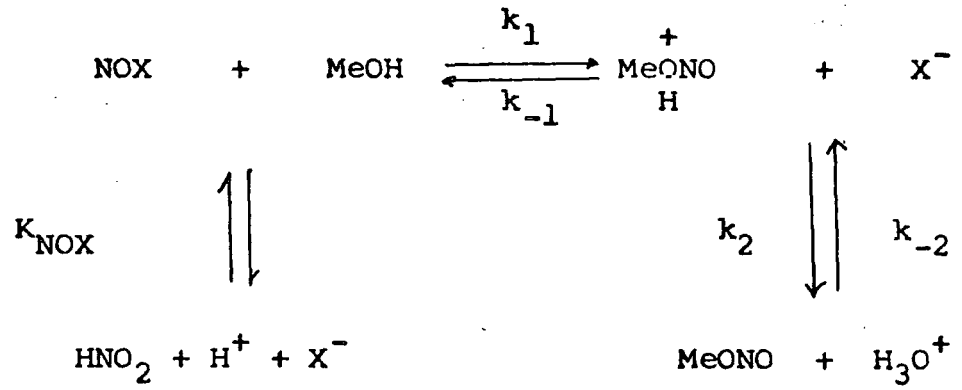
Table 4.30 methyl nitrite formation; catalysis by bromide ion

[LiBr],M	k_o, s^{-1}
0.065	5.63 ± 0.20
0.130	5.88 ± 0.21
0.259	6.24 ± 0.14
0.389	6.62 ± 0.36

Graphs of k_o against the total added chloride concentration and the lithium bromide concentration were plotted and were found to give reasonable straight lines. It can be seen that the reaction is subject to chloride ion and bromide ion catalysis although the amount of the catalysis is rather low. Woppmann and Sofer[39] have estimated the equilibrium constants K_{NOX} for the formation of nitrosyl halides in methanol (equation 4.9) to be 2.03(for nitrosyl bromide) and 5.05 $x10^{-2}$(for nitrosyl chloride) l^2mol^{-2} at 0^oC. These values indicate that both nitrosyl chloride and nitrosyl bromide are more stable in methanol than in water and on this basis a greater amount of catalysis would have been expected.

An outline of the proposed mechanism based upon the assumption that the reaction is analogous to the reaction in water is given in Scheme 4.2. In such a mechanism the rate expression would be predicted as equation 4.10

$$\text{rate} = \frac{k_1 k_2 K_{NOX}[HNO_2][MeOH][H^+][X^-]}{k_{-1}[X^-] + k_2} \qquad 4.10$$



Scheme 4.2

If the value of $(k_{-1}[X^-])$ is significantly larger than the rate constant k_2, then the amount of halide ion catalysis would be expected to be reduced or may totally disappear. The rate constant k_o was found to increase by ca. 17% going from 0.06 to 1.0M with respect to the total chloride concentration. The increases are small, within the limits of experimental error in some cases. It is possible that these increases could be due to salt effects rather than true halide ion catalysis. A similar situation has been reported by Hallett and Williams for the nitrosation of N-methylurea[120].

It was intended to examine the possibility of the catalysis of the nitrosation of methanol by nucleophiles other than chloride ion and bromide ion - in particular iodide ion and thiocyanate ion. However, problems with side reactions and the insolubility of salts prevented such studies from being undertaken.

4.3 Experimental.

4.3.1 Reactions of n-propyl nitrite in n-propanol.

synthesis of n-propyl nitrite. n-Propyl nitrite was prepared from n-propanol and sodium nitrite by the method used by Noyes[69] for the synthesis of alkyl nitrites. The crude product was purified by collecting the middle fraction obtained by careful distillation at atmospheric pressure (b.p. 49.0°C, lit. 48.9 - 49.4°C, Cowley and Partington[124]). The purified n-propyl nitrite was stored in a refrigerator.

Other reagents. Aniline and N-methyl aniline , obtained commercially, were purified by distillation at reduced pressure. p-Nitroaniline was recrystallised from aqueous ethanol.

Hydrogen chloride was dried by bubbling through concentrated sulphuric acid immediately before use. Tetraethylammonium chloride was dried in a vacuum desiccator.

Sulphuric acid, n-propanol and thiourea were obtained as analytical grade reagents and were used as supplied. Lithium chloride and lithium bromide were obtained as standard laboratory reagents and were used without further purification.

Rate measurements. All solutions were made up in 'Analar' n-propanol. A standard solution of the n-propyl nitrite was placed in a 31°C thermostat bath together with a flask containing 25cm^3 of a solution containing all other reagents. Reactions were started by pipetting 1cm^3 of the n-propyl nitrite solution into the solution containing the other reagents. After this addition the solution was agitated and rapidly transferred to a stoppered quartz cell which was

then placed in the cell compartment (thermostatted at 31°C) of a Beckman 25 or Pye Unicam SP 8-100 spectrophotometer. The progress of the reaction was monitored by following the appearance of the diazonium ion or nitrosamine at a suitable wavelength. The selected wavelengths were 290nm (310nm for the thiourea catalysed reactions) for the aniline and N-methylaniline reactions and 285nm for the diazotisation of p-nitroaniline. The amine concentration was always present in large excess (i.e. > 10 fold) over the n-propyl nitrite and good linear correlations were obtained for graphs of $-\ln(A_\infty - A_t)$ against time, thus indicating good first order behaviour. The observed rate coefficients, k_o, generally had a standard deviation of approximately $\pm$ 2% and duplicate runs were in good agreement. A typical kinetic run is given in table 4.31 overleaf. Correlations between k_o and reagent concentrations were based on the least squares principle.

Table 4.31

A_t	$-\ln(A_\infty - A)$	t, s
.225	.644	0
.287	.770	6
.348	.911	12
.398	1.044	24
.442	1.178	30
.482	1.317	36
.518	1.461	42
.550	1.609	48
.572	1.726	54
.595	1.865	60
.750	-	∞

$[NMA] = 1.497 \times 10^{-3}M$

$[H_2SO_4] = 3.46 \times 10^{-2}M$

$[\dot{n}PrONO] = 1.36 \times 10^{-4}M$

$[LiBr] = 2.19 \times 10^{-2}M$

$k_o = 2.28 \times 10^{-2}, s^{-1}$

4.3.2 Formation of methyl nitrite in methanol.

Reagents.Sodium nitrite, lithium chloride and lithium bromide were obtained as standard laboratory reagents and were used without further purification. Analytical grade methanol and sulphuric acid were used. Hydrogen chloride was dried by passing through concentrated sulphuric acid before use. All solutions were made up in 'Analar' methanol.

Rate measurements. Kinetic measurements were made by mixing two thermostatted solutions (one containing sodium nitrite, the other containing all other reagents) in the cell of a Canterbury SF-3A stopped-flow spectrophotometer. The details of the stopped-flow method are given in Chapter 2 of this thesis. The change in absorbance at 386nm was monitored. All kinetic runs were repeated five times and the mean rate coefficient of these runs was taken as the first order rate constant k_o. The methanol was, of course, present in vast excess over the sodium nitrite and good first order plots were obtained.

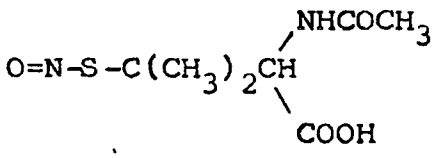
CHAPTER FIVE.

THE S-NITROSATION OF N-ACETYL (D,L) PENICILLAMINE.

5.1 Introduction.

The preparation of thionitrites (or nitrosothiols) from the reaction between a thiol and a nitrosating agent is well known[90,89]. Thionitrites are generally rather unstable compounds. However, two unusually stable thionitrites are known - trityl thionitrite and N-acetyl S-nitroso (D,L) penicillamine (I). Field and co-workers have been able to determine the structure of N-acetyl S-nitroso (D,L) penicillamine by X-ray crystallography.[91] Most thionitrites are dark red in colour,[92] but the two stable ones mentioned above are dark green

I



Until recently the kinetics and mechanisms of reactions involving S-nitrosation and thionitrite formation have received little attention. However since the discovery of the catalysis of N-nitrosation and denitrosation by thiourea and thiocyanate ion (reactions in which S-nitroso species are believed to be involved) the study of S-nitrosation has received rather more attention.

Stedman and co-workers have made studies of the reaction of nitrous acid with thiourea[93] and some alkyl substituted alkylthioureas[95]. In these reactions S-nitroso-thiourea cations are believed to form and then decompose to yield the products of the reaction.

It would be of interest to make a comparison between the alkyl nitrite and thionitrite systems and in this part

of this thesis the kinetics of nitrosation of the thiol N-acetyl (D,L) penicillamine are investigated. N-acetyl (D,L) penicillamine was selected as the most convenient thiol to nitrosate; its S-nitroso derivative is relatively stable and the thionitrite is formed rapidly in dilute aqueous acid solutions.

5.2 The acid catalysed reaction.

In the absence of added nucleophiles the formation of N-acetyl S-nitroso (D,L) penicillamine from the thiol and nitrous acid in dilute aqueous perchloric acid was followed by monitoring the formation of the thionitrite (at 338nm, the maximum of the broad thionitrite peak) using conventional spectroscopic techniques or by the stopped-flow method. Reactions were carried out at 31°C using a large excess of the thiol (> 10 fold) so that reactions were of the first order. All kinetic runs showed excellent first order behaviour with respect to the initial nitrite concentration (a typical set of results is given in table 5,11 in the experimental section of this chapter). The variation of the first order rate constant, k_o, with the N-acetyl (D,L) penicillamine concentration and the acidity was studied.

5.2.1. Variation of k_o with the thiol concentration.

Using reactant conditions of $[NaNO_2] = 1.198 \times 10^{-4}M$, $[HClO_4] = 9.50 \times 10^{-3}M$, the first order rate constant k_o was determined at two concentrations of N-acetyl (D,L) penicillamine.

The results are shown in table 5.1 and they clearly show that doubling the thiol concentration produced a two-fold increase in the rate constant k_o i.e. that there is a first order dependence of k_o upon the thiol concentration.

Table 5.1 dependence of k_o on [thiol].

[thiol] $x10^3$,M	k_o $x10^2$, s^{-1}
2.403	2.94 $\pm$ 0.07
4.806	6.14 $\pm$ 0.15

For the acidity of these experiments the nitrosation reaction appears to be irreversible; a plot of the two points in table 5.1 produces a straight line through the origin. Moreover, the infinity absorbances were almost the same, irrespective of the penicillamine concentration. Here, therefore, there is a significant difference between the nitrosation of N-acetyl (D,L) penicillamine and the alcohol systems. The formation of alkyl nitrites were clearly reversible, plots of k_o against the alcohol concentration had large positive intercepts on the y-axis.

In another study[125] it has been demonstrated that the reverse reaction only becomes important at much higher acidity. It was found that rate measurements could be made using solutions of ca. 1-4M with respect to sulphuric acid.

5.2.2 variation of k_o with acidity.

Two series of experiments on the acid catalysis of the formation of the thionitrite were performed. The results are presented in tables 5.2 and 5.3. Both sets of results showed a good linear correlation between k_o and the

hydrogen ion concentration (figure 1). The results also showed that graphs of k_o against the hydrogen ion concentration had a significant positive intercept on the y-axis. This may be interpreted on the basis of general acid catalysis by the N-acetyl (D,L) penicillamine.

Table 5.2 acid catalysis of thionitrite formation.

[penicillamine] = 3.679×10^{-3}M

[$NaNO_2$] = 3.735×10^{-4}M

[$HClO_4$] $\times 10^3$,M	$[H^+]_{xs} \times 10^3$,M	$k_o \times 10^2$,s^{-1}
3.70	3.33	1.97
7.40	4.03	3.07
11.10	10.73	4.24
14.80	14.43	5.30

slope = 3.02 ± 0.04 1 mol^{-1} s^{-1}

intercept = 0.086 ± 0.004 s^{-1}

Table 5.3 acid catalysis of thionitrite formation.

[penicillamine] = 3.691×10^{-3}M

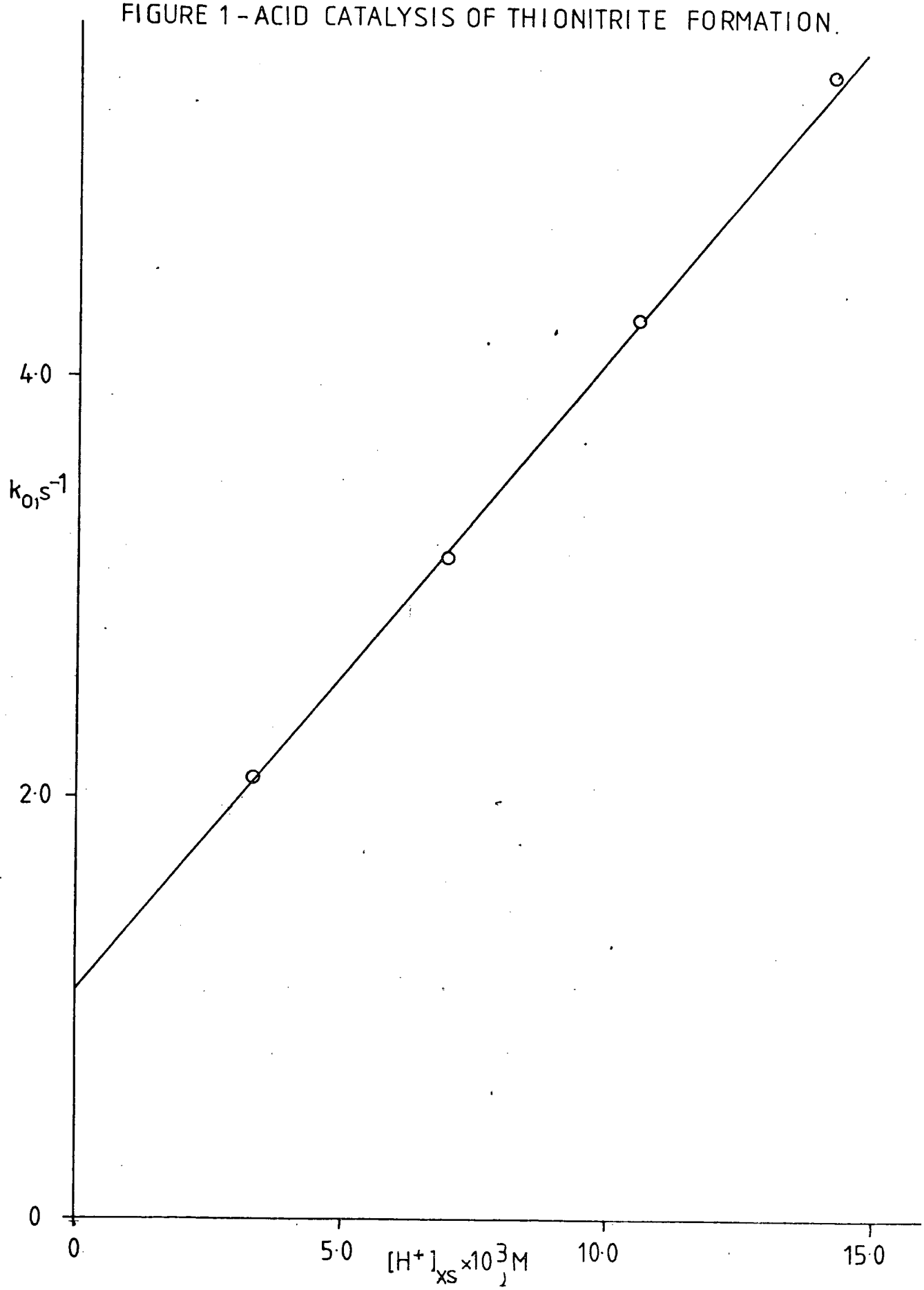
[$NaNO_2$] = 3.623×10^{-4}M

[$HClO_4$] $\times 10^3$,M	$[H^+]_{xs} \times 10^3$,M	$k_o \times 10^2$, s^{-1}
3.64	3.28	2.10
7.29	6.93	3.14
10.94	10.57	4.27
14.58	14.22	5.42

slope = 3.04 ± 0.06 1 mol^{-1} s^{-1}

intercept = 0.0108+ 0.006 s^{-1}

FIGURE 1 - ACID CATALYSIS OF THIONITRITE FORMATION.



The first order experimentally determined rate constant, k_o, may be defined by equation 5,1

$$\frac{d[RSNO]}{dt} = k_o[HNO_2] \qquad 5.1$$

A probable mechanism for the reaction is outlined in Scheme 1 and in this mechanism it is proposed that the S-nitrosation is the rate determining step. The nitrosating agent would most probably be the nitrous acidium ion for the experimental conditions used in this study, or could perhaps be NO^+ but this is thought to be less likely since there would only be exceedingly low concentrations of the nitrosyl cation at such low acidity.

$$HNO_2 + H^+ \rightleftharpoons H_2NO_2^+$$

$$H_2NO_2^+ + RSH \xrightarrow{k_2} RS\overset{+}{\underset{H}{N}}O + H_2O$$

$$RS\overset{+}{\underset{H}{N}}O \rightleftharpoons RSNO + H^+$$

Scheme 1

It is possible to express the rate of reaction in terms of the concentration of N-acetyl (D,L) penicillamine and the acidity (equation 5.2).

$$\text{rate} = k_2[\text{penicillamine}][H^+][HNO_2] \qquad 5.2$$

From equation 5.2 k_o may be expressed in terms of the penicillamine and hydrogen ion concentrations:

$$k_o = k_2[RSH][H^+] \qquad 5.3$$

From the experimental data in tables 5.2 and 5.3 the values of k_2 were determined as 820 ± 10 and 822 ± 15 $l^2mol^{-2}s^{-1}$.

As stated earlier, in Chapter 2, the rate constants for the diffusion controlled nitrosation of various substrates by the nitrous acidium ion average at approximately 640 $l^2mol^{-2}s^{-1}$ in aqueous solution at 0^oC. The values of k_2 for the S-nitrosation of N-acetyl (D,L) penicillamine determined at 31^oC indicated that the S-nitrosation of this tertiary thiol is rapid but does not fall into the class of diffusion controlled processes.

In order to draw a comparison between O-nitrosation and S-nitrosation the third order rate constants for the nitrosation of t-butanol and N-acetyl (D,L) penicillamine could be considered. The third order rate constant for the O-nitrosation of t-butanol could not be determined but was certainly much less than that for i-propanol. Therefore it is probably less than 10 $l^2mol^{-2}s^{-1}$ at 31^oC. The third order rate constant for the nitrosation of N-acetyl (D,L) penicillamine is ca. 100 times greater than that for t-butanol. It would appear, therefore, that the third order rate constant for the S-nitrosation of a tertiary thiol is much larger than the corresponding third order rate constant for O-nitrosation. This observation reflects the greater nucleophilicity of the sulphur atom compared to the oxygen atom, the sulphur atom being rather more polarisable than the oxygen.

Stedman has made a detailed investigation into the S-nitrosation of thiourea and its derivatives. The study was also extended to include the nitrosation of the thiol cysteine[95]. Stedman found that solutions of cysteine and nitrous acid gave a similar spectrum to solutions of thiourea

and nitrous acid. In the absence of halide ions the following rate equation was established:

$$\text{rate} = k[HNO_2][H^+][\text{cysteine}]$$

This is identical to the rate expression found for the nitrosation of N-acetyl (D,L) penicillamine. Stedman concluded that the reaction was one of S-nitrosation leading to the formation of an unstable thionitrite, which was not isolated. The results also strongly indicated that the equilibrium between the thiol, nitrous acid and the thionitrite was far on the side of the thionitrite. The rate data also suggest that whilst the nitrosation of thiourea by the nitrous acidium ion appeared to be subject to diffusion control, the nitrosation of cysteine by the same nitrosating agent appeared to take place at a rate that was rather lower than the rate of encounter. This was suggested to be a result of electrostatic interactions between the amino acid and the nitrous acidium ion.

By comparing Stedman's results for the nitrosation of the thioureas with the results in the present study for the nitrosation of N-acetyl (D,L) penicillamine it appears that the penicillamine derivative is ca. 10 times less reactive than the thioureas.

5.3 The nucleophilic catalysis of the nitrosation of N-acetyl (D,L) penicillamine.

Experiments indicated that the addition of nucleophiles had a catalytic effect upon the nitrosation of N-acetyl (D,L) penicillamine in aqueous acidified sodium nitrite solutions. The catalytic effect of various nucleophiles was therefore studied in greater detail.

As in the case of the acid catalysed reaction in the absence of nucleophiles kinetic runs were followed by conventional or stopped-flow spectrophotometry. Rate measurements were again determined by monitoring the change in absorbance at 338nm. Series of kinetic runs were carried out in the presence of chloride ions, bromide ions, thiocyanate ions and iodide ions. The catalysis of the reaction by thiourea was also attempted,but without success on account of practical difficulties arising from extensive side reactions which prevented the determination of rate constants. The results of kinetic runs in the presence of nucleophiles are presented in tables 5.4, 5.5, 5.6 and 5.7.

Table 5.4 catalysis by chloride ions.

$[NaCl] \times 10^2$, M	$k_o \times 10^2$, s^{-1}
0	2.72
1.92	3.23
4.81	3.19
9.61	3.90
19.21	4.47

$[penicillamine] = 3.679 \times 10^{-3}$M

$[HClO_4] = 7.40 \times 10^{-3}$M

$[NaNO_2] = 3.735 \times 10^{-4}$M

FIGURE 2 - HALIDEION CATALYSIS OF THIONITRITE FORMATION.

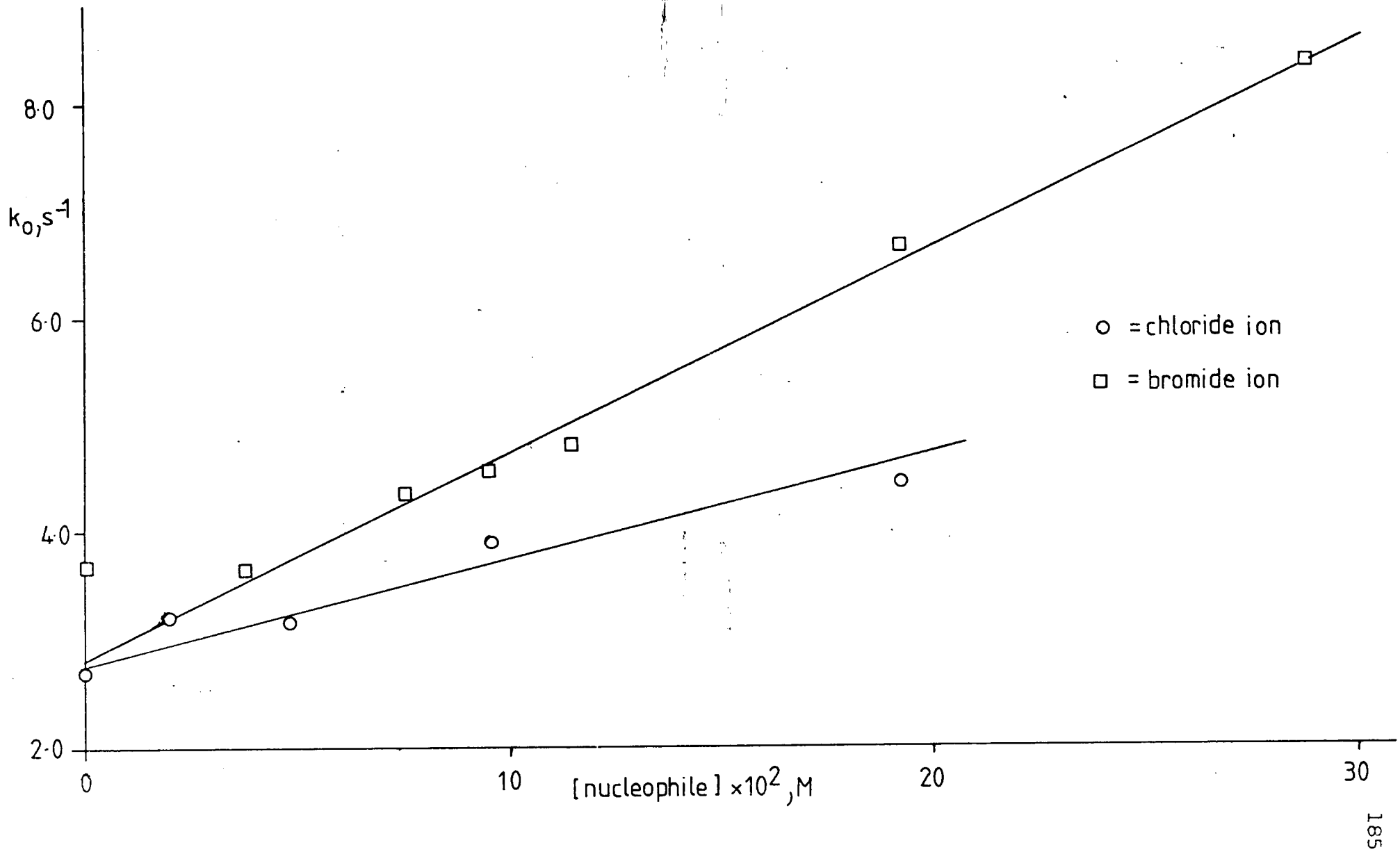


Table 5.5 catalysis by bromide ions.

$[NaBr]\ x10^{2}, M$	$k_o\ x10^{2}, s^{-1}$
0	3.72
3.83	3.62
7.66	4.37
9.62	4.57
11.49	4.79
19.25	6.69
28.88	8.38

$[RSH] = 3.679\ x10^{-3} M$

$[HClO_4] = 7.40\ x10^{-3} M$

$[NaNO_2] = 3.735\ x10^{-4} M$

Table 5.6 catalysis by thiocyanate ions.

$[NaSCN]\ x10^{2}, M$	k_o, s^{-1}
0	2.76
0.736	3.58
1.472	4.87
2.943	5.94
4.416	6.62
8.829	7.36

$[RSH] = 2.354\ x10^{-3} M$

$[HClO_4] = 9.50\ x10^{-3} M$

$[NaNO_2] = 1.557\ x10^{-4} M$

Table 5.7 catalysis by iodide ions.

$[NaI] \times 10^2$, M	$k_o \times 10^2$, s^{-1}
0	2.94
0.502	4.08
1.005	6.44
2.011	10.37
3.015	10.82
4.022	10.92

$[RSH] = 2.403 \times 10^{-3}$M

$[HClO_4] = 9.50 \times 10^{-3}$M

$[NaNO_2] = 1.199 \times 10^{-4}$M

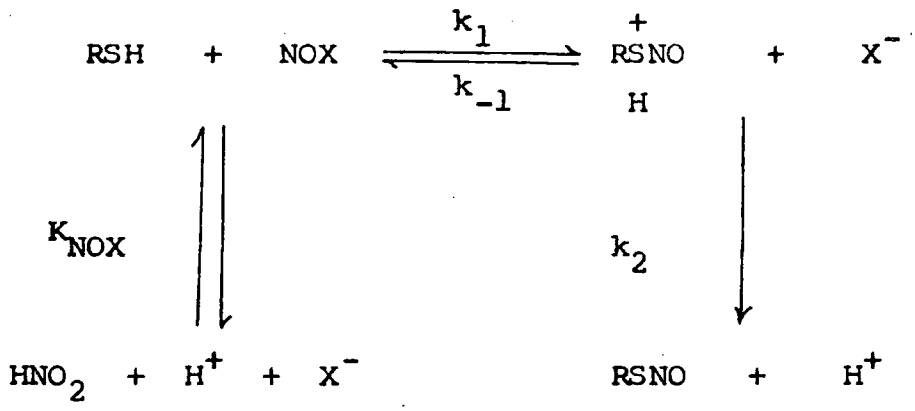
The tables of results show that the extent of the catalysis is significant and the catalytic effect of the nucleophiles followed the sequence:

$$Cl^- < Br^- < SCN^- < I^-$$

The data for the chloride ion and bromide ion catalysis are also shown in the graph in figure 2. It can be seen that a linear correlation exists between k_o and the concentrations of these two halide ions. However, in the cases of the thiocyanate ion and iodide ion catalysed reactions, plots of k_o against the nucleophile concentration showed a distinct tendency to level-off at high nucleophile concentrations to give, in the case of the iodide ion catalysed reaction, k_o(max) of ca. 11 $\times 10^{-2}$ s^{-1}.

It is most likely that the reaction involves the nitrosyl halide or nitrosyl thiocyanate as the effective nitrosating agent; this also appeared to be the case for the halide ion catalysed nitrosation of alcohols.

The observations on the nucleophilic catalysis of the nitrosation of the penicillamine derivative may be accounted for on the basis of a mechanism in which the initial S-nitrosation of the thiol by the nitrosyl halide (or nitrosyl thiocyanate) is reversible. The reversible nature of nitrosations by nitrosyl halides has been proposed in the past in order to account for the observations on the diazotisation of anilines in water[32] and in methanol solvent[39]. Such a mechanism for the nitrosation of the N-acetyl (D,L) penicillamine is outlined in Scheme 5.2 below:



Scheme 5.2.

Although it appears surprising that attack of the nucleophile X^- upon the intermediate protonated thionitrite could compete with the loss of a proton from this intermediate to the solvent this does seem to be the most satisfactory explanation of the experimental observations.

The observed first order rate constant k_o for Scheme 5.2 is defined:

$$-\frac{d[HNO_2]}{dt} = k_o[HNO_2]$$

and may be expressed in terms of the rate constants in Scheme 5.2 and the uncatalysed reaction (equation 5.4)

$$k_o = k_{HNO_2}[RSH][H^+] + \frac{k_1 k_2 K_{NOX}[RSH][H^+][X^-]}{k_{-1}[X^-] + k_2} \qquad 5.4$$

The term for the uncatalysed reaction was obtained for each reaction at zero nucleophile concentration. The value of k_{HNO_2} was found to be 1130 $\pm$ 150 $l^2 mol^{-2} s^{-1}$ from the k_o values in the absence of nucleophiles for each set of results. The value of k_{HNO_2} is somewhat larger than the values determined earlier (ca. 820 $l^2 mol^{-2} s^{-1}$) for no apparent reason. K_{NOX} is the equilibrium constant for the formation of the nitrosyl halide or nitrosyl thiocyanate and is known for nitrosyl chloride[27], nitrosyl bromide[28] and nitrosyl thiocyanate[127].

In the case of the chloride ion and bromide ion catalysed reactions it appears that the condition

$$k_2 \quad >> \quad k_{-1}[X^-]$$

applies and hence plots of k_o against the nucleophile concentration were linear since equation 5.4 would then reduce the equation 5.5.

$$k_o = k_{NNO_2}[RSH][H^+] + k_1 K_{NOX}[RSH][H^+][X^-] \qquad 5.5$$

The values of k_2 were calculated for the chloride ion and bromide ion catalysed reactions and found to be 2.6 $x10^6$ $l\ mol^{-1} s^{-1}$ and 1.4 $x10^5$ $l\ mol^{-1} s^{-1}$ respectively. The relative reactivities are about the same as found for the nitrosation of alcohols by these nitrosyl halides.

For the thiocyanate ion and iodide ion catalysis the

equation 5.5 did not apply but equation 5.4 appeared to apply. The reciprocal of equation 5.4 indicates that a plot of $(k_o - k_{HNO_2}[RSH][H^+])^{-1}$ against $([X^-])^{-1}$ should be linear and the value of the rate constant k_1 could be obtained from the slope of the graph. The data for these graphs are given in tables 5.8 and 5.9 (in these graphs $k_o' = k_o - k_{HNO_2}[RSH][H^+]$).

Table 5.8 thiocyanate ion catalysis.

$([SCN^-])^{-1}$	$(k_o')^{-1}$
11.3	22
22.6	26
34.0	31
67.9	47
136	123

slope = 0.842 ± 0.048

intercept = 7.6 ± 3.4

Table 5.9 iodide ion catalysis.

$([I^-])^{-1}$	$(k_o')^{-1}$
24.9	12.5
33.2	12.7
49.7	13.4
99.5	28.5
199	87.6

slope = 0.226 ± 0.045

intercept = 5.08 ± 2.55

From these plots, which gave reasonable straight lines, k_2 for the thiocyanate ion catalysis was found to be 3.0×10^3 l $mol^{-1}s^{-1}$. The value of the equilibrium constant for the formation of nitrosyl iodide is not known and so the rate constant k_2 could not be evaluated for the iodide ion catalysed reaction.

The catalysis of nitrosation reactions by thiocyanate ion is now well established[33] although much less work on such catalysis has been done than the corresponding bromide ion and chloride ion catalysed reactions. Stedman demonstrated that nitrosyl thiocyanate was actually much less reactive than either nitrosyl bromide or nitrosyl chloride for the nitrosation of hydroxylamine and O-methylhydroxylamine[126] and more recently, similar conclusions were reached for the nitrosation of morpholine and the diazotisation of aniline[35]. The greater extent of catalysis of thiocyanate ion compared to bromide ion is therefore a result of the much larger equilibrium constant for the formation of the nitrosyl thiocyanate than that for the nitrosyl bromide. The results for the nitrosation of N-acetyl (D,L) penicillamine are also consistent with the nitrosation of nitrosyl thiocyanate being less reactive than nitrosyl bromide by a factor of ca. 50.

The rate constants for the nitrosation of N-acetyl (D,L) penicillamine by nitrosyl halides and nitrosyl thiocyanate are well below the values for aniline[32,35] (table 5.10). The values for the nitrosation of aniline by the nitrosyl halides are approaching the limit of a diffusion controlled

process.

However, the overall difference between the k values for aniline and the thiol will not be as large as indicated in the table because in the dilute aqueous acid solutions aniline is protonated to a large extent whereas the thiol will be protonated to a much lesser extent. One would conclude, however, that for the reaction conditions used in the present study the nitrosation of N-acetyl (D,L) penicillamine by nitrosyl halides or nitrosyl thiocyanate is rapid but is not subject to diffusion control.

Table 5.10 rate constants for nitrosation by NOX

NOX	substrate	k_2 1 $mol^{-1}s^{-1}$	T°C
NOCl	aniline[32]	2.2×10^9	25
	RSH	2.6×10^6	31
NOBr	aniline[32]	1.7×10^9	25
	RSH	1.4×10^5	31
NOSCN	aniline[35]	1.1×10^7	31
	RSH	3.0×10^3	31

5.4 the use of N-acetyl S-nitroso (D,L) penicillamine as a nitrosating agent.

The formation of the S-nitroso species from solutions of N-acetyl (D,L) penicillamine containing an acid and sodium nitrite has been established. Recently, it has been demonstrated that certain sulphur containing nucleophiles catalyse N-nitrosation reactions by forming the S-nitroso species which then act as the effective nitrosating agent[35]. In the present study it was decided to make a brief examination of the behaviour of N-acetyl S-nitroso (D,L) penicillamine as a nitrosating agent in a reaction involving N-nitrosation with the aim of determining whether the thionitrite behaved as a direct or an indirect nitrosating agent.

The diazotisation of p-nitroaniline was selected as a suitable reaction. N-acetyl S-nitroso (D,L) penicillamine was prepared following the method described by Field et alia[91]. The diazotisation reaction was carried out in aqueous sulphuric acid solutions containing the thionitrite. Spectra in the region 260 - 360 nm were recorded for a solution containing no added nitrite trap and for a solution containing an excess of sodium azide.

It was found that the addition of sodium azide could completely suppress the diazotisation reaction, suggesting that the N-acetyl S-nitroso (D,L) penicillamine was behaving as an indirect nitrosating agent.

5.5 Experimental.

5.5.1 reagents.

N-acetyl (D,L) penicillamine was obtained commercially (Sigma) and was used without further purification. It was stored in a refrigerator. Perchloric acid solutions were prepared by dilution of 60-62% perchloric acid and standardised against sodium hydroxide using phenol red as the endpoint indicator. All other reagents were of the highest purity grade available (generally analytical reagent grade) and were used as supplied. N-acetyl (D,L) penicillamine solutions were freshly prepared when required.

5.5.2 kinetic measurements.

Rate measurements were made by following the absorbance change at 338nm in the cell of a conventional spectrophotometer (Beckman 25 or Pye-Unicam SP 8-100) or by means of a stopped-flow spectrophotometer. Kinetic measurements were carried out at a temperature of 31^{o}C.

In the case of reactions studied by conventional spectrophotometry, two solutions were thermostatted - one containing a stock solution of sodium nitrite, the other containing all other reagents and having a total volume of 25cm^3. Kinetic runs were started by adding 1cm^3 of the sodium nitrite solution to the solution of all the other reagents, mixing the contents of the flask and then transferring a portion to the 1cm quartz cell which was then placed in the cell holder of the spectrophotometer.

The stopped-flow method was described in Chapter 2.

All kinetic measurements were carried out under first order conditions and in all cases good first order plots (of ln ($A_\infty - A_t$) against time) were obtained over several half-lives. A typical kinetic run is shown in table 5.11 below:

Table 5.11 a typical kinetic run for the nitrosation of N-acetyl (D,L) penicillamine.

$[HClO_4] = 3.7 \times 10^{-3}M$

$[RSH] = 3.679 \times 10^{-3}M$

$[NaNO_2] = 3.735 \times 10^{-4}M$

A	$-\ln(A_\infty - A_t)$	t,sec
0.138	1.640	0
0.168	1.790	12
0.207	2.079	24
0.232	2.303	36
0.253	2.538	48
0.270	2.781	60
0.283	3.016	72
0.294	3.270	84
0.332	-	∞

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APPENDIX

A) LECTURES AND SEMINARS ORGANISED BY THE DEPARTMENT OF CHEMISTRY DURING THE PERIOD 1978-1981.

(- denotes those seminars attended)

15 September 1978

Professor W. Siebert (University of Marburg,W. Germany)

"Boron Heterocycles as ligands in Transition Metal Chemistry".

22 September 1978

Professor T. Fehlner (University of Notre Dame,USA)

"Ferraboranes: Syntheses and Photochemistry".

- 12 December 1978

Professor C.J.M. Sterling (Bangor)

" 'Parting is such sweet sorrow' - the leaving group in Organic Reactions".

14 February 1979

Professor B. Dunnel (University of British Columbia)

"The Application of NMR to the study of Motions in Molecules".

16 February 1979

Dr. J. Tompkinson (Institute of Laue-Langevin,Grenoble)

"Properties of Adsorbed Species".

14 March 1979

Dr. J.C.Walton (St. Andrews)

"Pentadienyl Radicals".

20 March 1979

Dr. A. Reiser (Kodak Ltd.)

"Polymer Photography and Mechanism of Cross-link Formation in Solid Polymer Matrices".

25 March 1979

Dr. S. Larsson (University of Uppsala).

"Some Aspects of Photoionisation Phenomena in Inorganic Systems".

- 25 April 1979

Dr. C.R. Patrick (Birmingham)

"Chlorofluorocarbons and Stratospheric Ozone: an Appraisal of the Environmental Problems".

1 May 1979

Dr. G. Wyman (European Research Office, US Army)

"Excited State Chemistry in Indigoid Dyes".

2 May 1979

Dr. J.D. Hobson (Birmingham)

"Nitrogen-centred Reactive Intermediates".

8 May 1979

Professor A. Schmidpeter (Institute of Inorganic Chemistry University of Munich)

"Five-membered Phosphorus Heterocycles Containing Dicoordinate Phosphorus".

- 9 May 1979

Dr. A.J. Kirby (Cambridge)

"Structure and Reactivity in Intramolecular and Enzymic Catalysis".

9 May 1979

Professor G. Maier (Lahn-Giessen)

"Tetra-tert-butyltetrahedrane".

10 May 1979

Professor G. Allen,F.R.S. (Science Research Council)

"Neutron Scattering Studies of Polymers".

16 May 1979

Dr. J.F. Nixon (Sussex)

"Spectroscopic Studies on Phosphines and their Coordination Complexes".

23 May 1979

Dr. B. Wakefield (Salford)

"Electron Transfer in Reactions of Metals and Organometallic Compounds with Polychloropyridine Derivatives".

13 June 1979

Dr. G. Heath (Edinburgh)

"Putting Electrochemistry into Mothballs - (Redox Processes of Metal Porphyrins and Phthalocyanines)".

14 June 1979

Professor I. Ugi (University of Munich)

"Synthetic Uses of Super Nucleophiles".

20 June 1979

Professor J.D. Corbett (Iowa State University, USA)

"Zintl Ions: Synthesis and Structure of Homo-polyatomic Anions of the Post-Transition Elements".

27 June 1979

Dr. H. Fuess (University of Frankfurt)

"Study of Electron Distribution in Crystalline Solids by X-ray and Neutron Diffraction".

21 November 1979

Dr. J. Muller (University of Bergen)

"Photochemical Reactions of Ammonia".

28 November 1979

Dr. B. Cox (Sterling)

"Macrobicyclic Cryptate Complexes, Dynamics and Selectivity".

5 December 1979

Dr. G.C. Eastmond (Liverpool)

"Synthesis and Properties of Some Multicomponent Polymers".

12 December 1979

Dr. C.I. Ratcliffe (London)

"Rotor Motions in Solids".

19 December 1979

Dr. K.E. Newman (University of Lausanne)

"High Pressure Multinuclear NMR in the Elucidation of the Mechanisms of Fast, Simple Reactions".

30 January 1980

Dr. M.J. Barrow (Edinburgh)

"The Structures of Some Simple Inorganic Compounds of Silicon and Germanium - Pointers to Structural Trends in Group IV".

6 February 1980

Dr. F.M.E. Quirke (Durham)

"Degradation of Chlorophyll-a in Sediments".

23 April 1980

B. Grievson B.Sc. (Durham)

"Halogen Radiopharmaceuticals".

14 May 1980

Dr. R. Hutton (Waters Associates, USA)

"Recent Developments in Multimilligram and Multi-gram Scale Preparative HPLC".

21 May 1980

Dr. T.W. Bentley (Swansea)

"Medium and Structural Effects in Solvolytic Reactions".

10 July 1980

Professor P. des Marteau (University of Heidelburg)

"New Developments in Organonitrogen Fluorine Chemistry".

7 October 1980

Professor T.Felhner (Notre-Dame University, USA)

"Metalloboranes - Cages or Coordination Compounds?".

15 October 1980

Dr. R. Adler (Bristol)

"Doing Chemistry Inside Cages - Medium Ring Bicyclic Molecules".

12 November 1980

Dr. M. Gerloch (Cambridge)

"Magnetochemistry is about Chemistry".

- 19 November 1980

Dr. T. Gilchrist (Liverpool)

"Nitroso Olefins as Synthetic Intermediates".

3 December 1980

Dr. J.A. Connor (Manchester)

"Thermochemistry of Transition Metal Complexes".

- 18 December 1980

Dr. R. Evans (University of Brisbane, Australia)

"Some Recent Communications to the Editor of the Australian Journal of Failed Chemistry".

18 February 1981

Professor S.F.A. Kettle (East Anglia)

"Variations in the Molecular Dance at the Crystal Ball".

25 February 1981

Dr. K. Bowden (Sussex)

"The Transmission of Polar Effects of Substituents".

4 March 1981

Dr.S. Craddock (Edinburgh)

"Pseudo-linear Pseudohalides".

11 March 1981

Dr. J.F. Stoddart (I.C.I./University of Sheffield)

"Stereochemical Principles in the Design and Function of Synthetic Molecular Receptors".

17 March 1981

Professor W. Jencks (Brandeis University,Massachusetts)

"When is an Intermediate not an Intermediate".

18 March 1981

Dr. P.J. Smith (International Tin Research Institute)

"Organotin Compounds - A Versatile Class of Organometallic Compounds".

9 April 1981

Dr. W.H. Meyer (RCA Zurich)

"Properties of Aligned Polyacetylene".

6 May 1981

Professor M. Szware F.R.S.

"Ions and Ion-pairs".

10 June 1981

Dr. J. Rose (I.C.I. Plastics Division)

"New Engineering Plastics".

17 June 1981

Dr. P. Moreau (University of Montpellier)

"Recent Results in Perfluoroorganometallic Chemistry".

B) FIRST YEAR INDUCTION COURSE, OCTOBER 1978

This course consists of a series of one hour lectures on the services available in the department.

1. Departmental organisation
2. Safety matters
3. Electrical appliances
4. Chromatography and microanalysis
5. Library facilities
6. Atomic absorption and inorganic analysis
7. Mass spectrometry
8. Nuclear Magnetic Resonance Spectroscopy
9. Glassblowing technique.